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OCTOBER 1976

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

14

Myocardial Imaging in Myocardial Infarction, Coronary Artery Disease and Left Bundle Branch Block

Treatment of Unstable Angina

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A YORKE MEDICAL JOURNAL

in hypertension

ALDOMET® 500 mg

(METHYLDOPA | MSD) 500-mg TABLETS



OFFERS B.I.D. CONVENIENCE WHEN HIGHER DOSAGE IS INDICATED

- **When appropriate.** ALDOMET 500-mg tablets may be useful when higher dosage (1.0 g to a maximum of 3.0 g a day) is required to control the blood pressure adequately.
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ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

For more details see the brief summary of prescribing information.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET®

(METHYLDOPA | MSD)

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood. At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped. Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

P24, 112

addendum

MSD MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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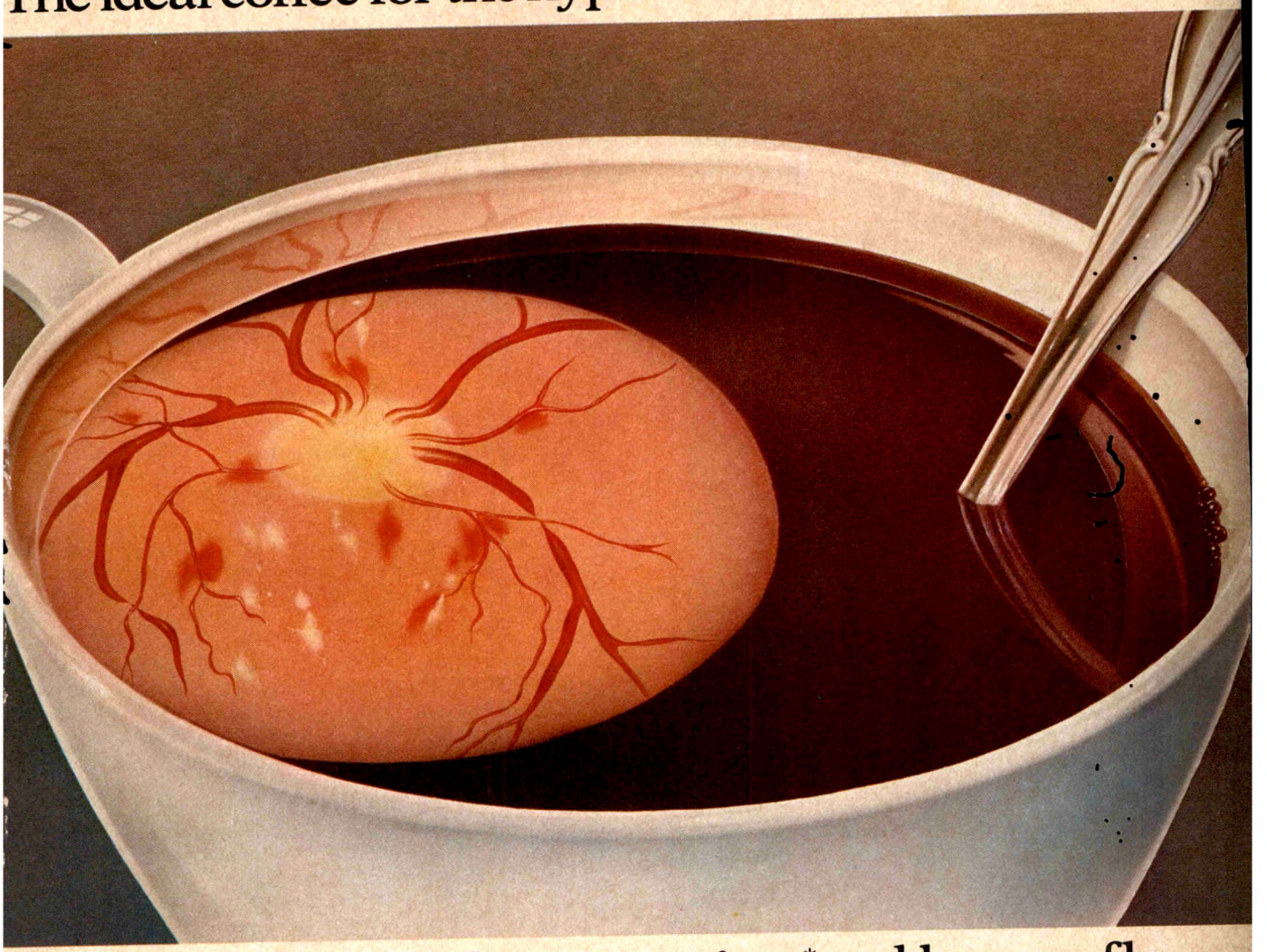
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Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

As with all quinidine preparations, the titrating of the exact quinidine dosage will vary with each individual patient. With the dosage regimen of 2 tablets every 8 hours, higher blood levels than necessary for maintenance of normal sinus rhythm could be reached, whereas with 1 tablet every 12 hours, the blood levels may be too low to maintain normal sinus rhythm.

As with other quinidine products, Quinaglute Dura-Tabs should not be used during pregnancy.

Adverse Reactions: The patient should be advised to report immediately to the physician any symptoms of cinchonism (including tinnitus, decreased auditory acuity, vertigo, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis and respiratory distress).

Where such symptoms develop, or if evidence of hypotension appears, the drug should be discontinued. Gastrointestinal disturbances have only rarely been reported. If they occur, they may be minimized by administering the drug with food. If they persist, dosage should be decreased.

Dosage: For the prevention of premature atrial, nodal or ventricular contractions, the dose usually ranges from 1 to 2 tablets every 8 or 12 hours.

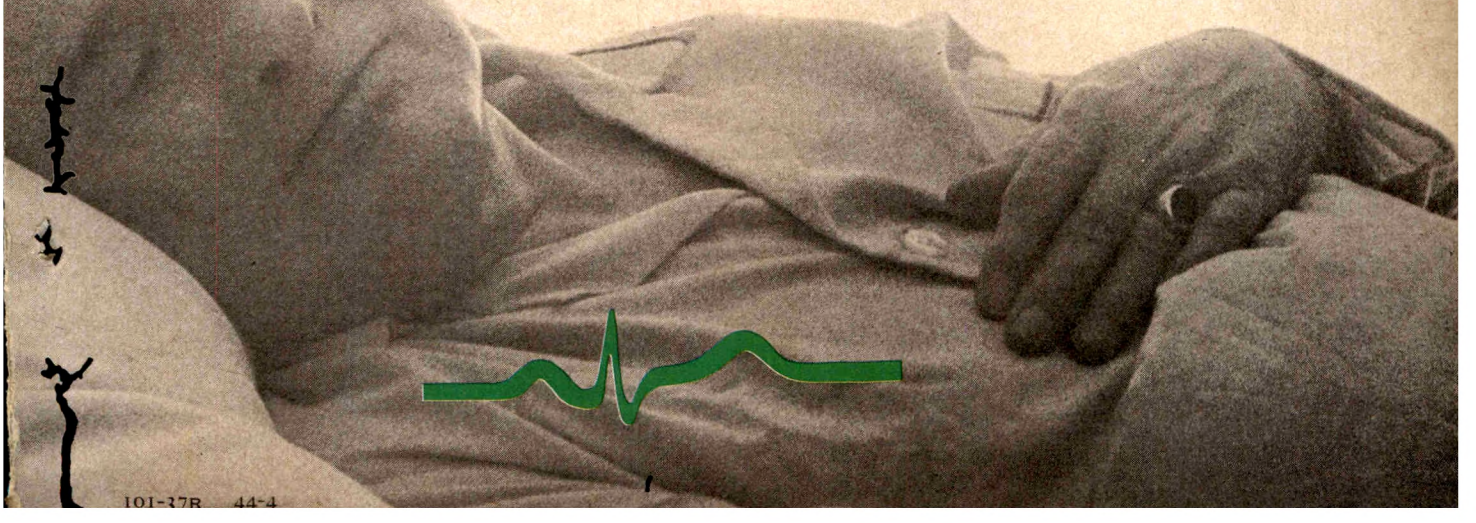
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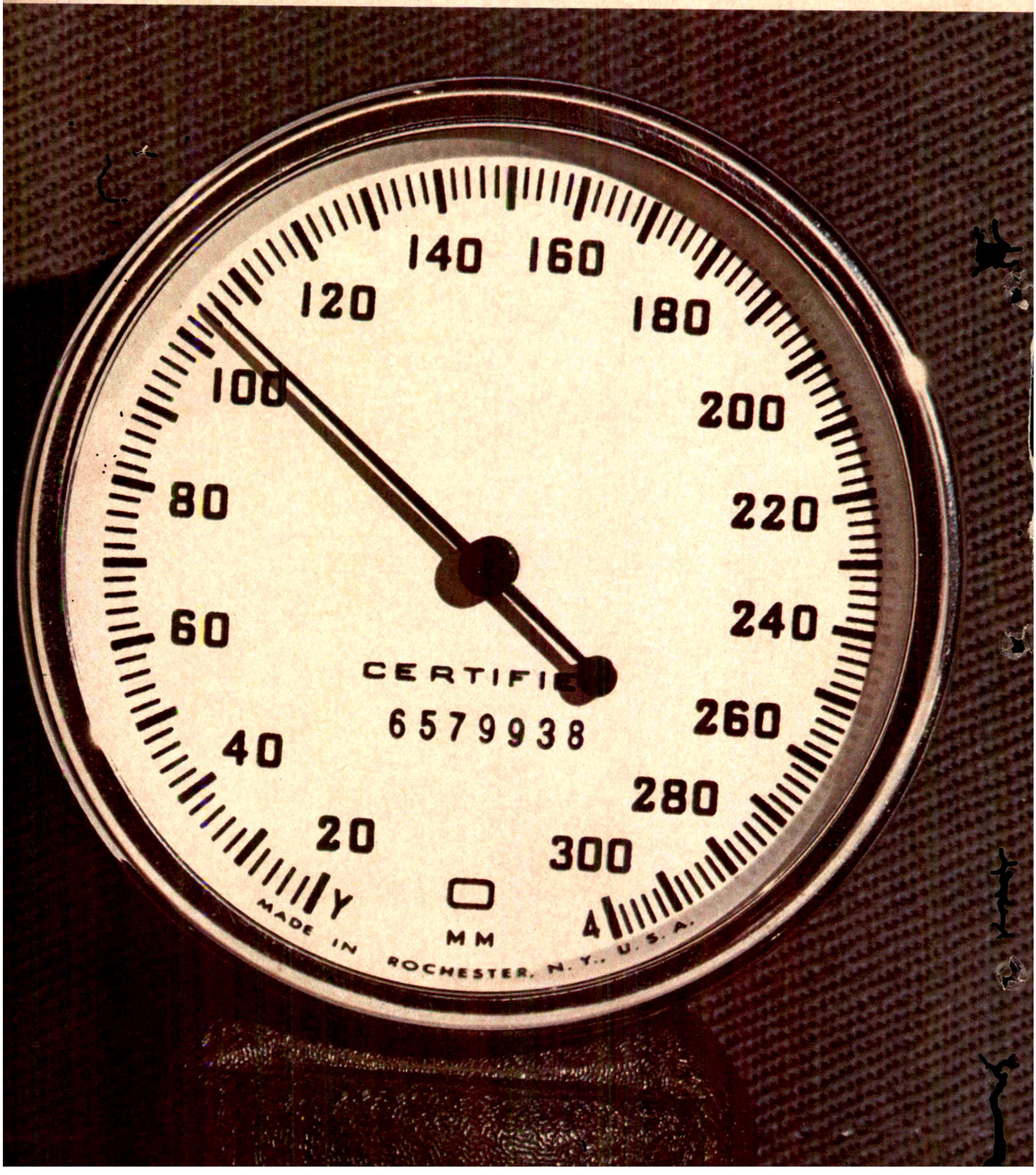
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The expense of K^+ rich foods and potassium supplements can cost your patient more than conventional antihypertensive diuretics. 'Dyazide' costs less than other K^+ -sparing agents.

SERUM K^+ AND BUN SHOULD BE CHECKED PERIODICALLY

Particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Elevated serum potassium levels can occur because of the potassium-sparing effect of 'Dyrenium', but they are rare in patients with normal renal function. If hyperkalemia develops, substitute a thiazide alone.

Use 'Dyazide' with caution during pregnancy or in women who might bear children; potential benefits should be weighed against possible hazards to the fetus.

SK&F CO.
Carolina, P.R. 00630
Subsidiary of
SmithKline Corporation

*'Dyazide' is not indicated for initial therapy. See next page for indications and brief summary of prescribing information.

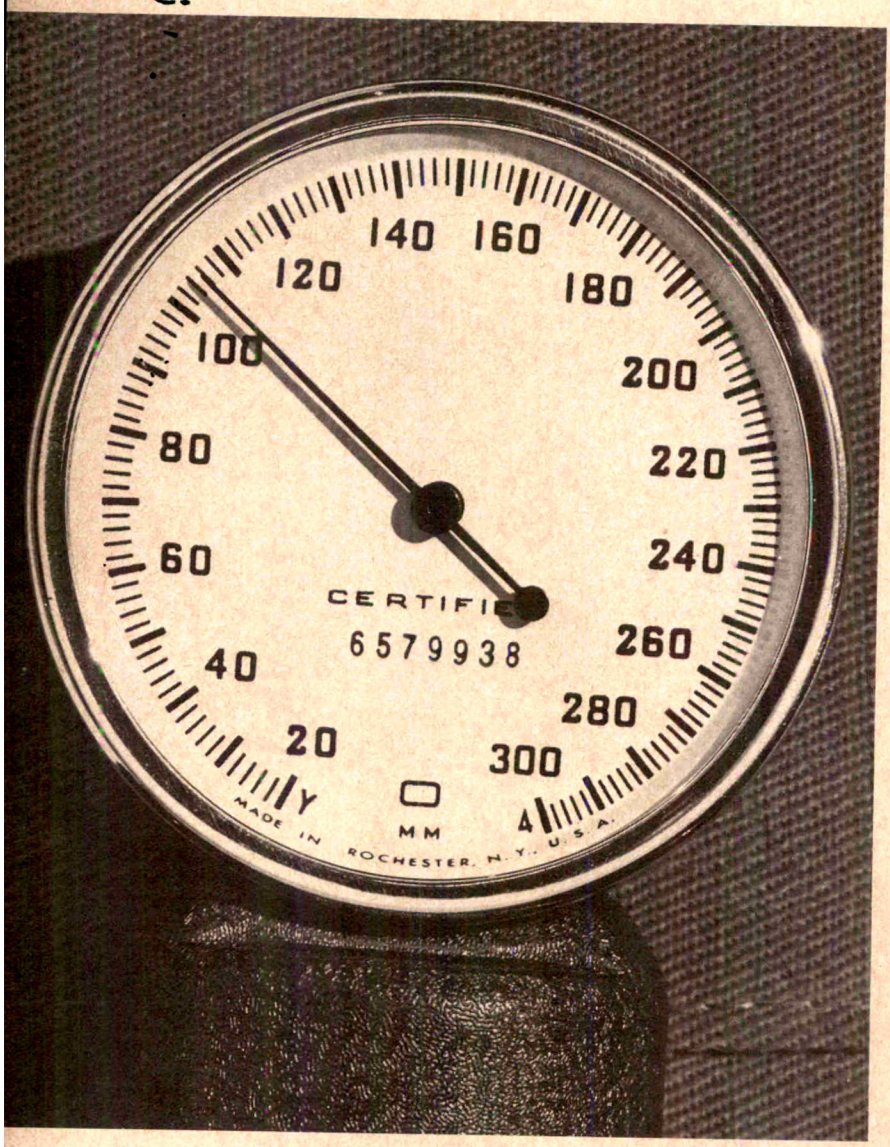
DYAZIDE®

Trademark

Each capsule contains 50 mg. of Dyrenium® (triamterene, SK&F Co.) and 25 mg. of hydrochlorothiazide.

IN HYPERTENSION

- CONVENIENT
- ECONOMICAL



SK&F CO.
Carolina, P.R. 00630
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SmithKline Corporation

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* **WARNING**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the fixed combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium-sparing action of its 'Dyrenium' component is warranted.

Contraindications: Further use in progressive renal or hepatic dysfunction; hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs. Routine use of diuretics in otherwise healthy pregnancy.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in severely ill patients with urine volume less than one liter/day, the elderly or diabetics, with suspected or confirmed renal insufficiency. Periodic determinations of serum K^+ should be made. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **The presence of a widened QRS complex or arrhythmia in association with hyperkalemia requires prompt additional therapy.** Thiazides are reported to cross the placental barrier and appear in breast milk; fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions that have occurred in the adult may result. When used in pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics, or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium® (triamterene, SK&F Co.), and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Do periodic blood studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

OCTOBER 1976

The American Journal of CARDIOLOGY

VOLUME 38

NUMBER 4

CONTENTS

CLINICAL STUDIES

407 Serial Measurements of Left Ventricular Ejection Fraction by Radionuclide Angiography Early and Late After Myocardial Infarction

HEINRICH R. SCHELBERT, HARTMUT HENNING, WILLIAM L. ASHBURN, JOHN W. VERBA, JOEL S. KARLINER and ROBERT A. O'ROURKE

Serial left ventricular ejection fraction measured with radioisotope angiography in 63 patients with acute myocardial infarction proved useful in patients with segmental left ventricular dysfunction and in predicting early mortality and morbidity. Data in this study show the ejection fraction is a sensitive indicator of left ventricular function after acute myocardial infarction.

416 Regional Myocardial Blood Flow During Hyperemia Induced by Contrasting Agent in Patients With Coronary Artery Disease

B. LEONARD HOLMAN, PETER F. COHN, DOUGLASS F. ADAMS, JACKIE R. SEE, BARBARA H. ROBERTS, JOHN IDOINE and RICHARD GORLIN

Measurements of regional myocardial specific blood flow at rest and during contrast hyperemia after the intracoronary injection of xenon-133 showed good correlation with the percent of coronary stenosis and the presence of ventricular wall abnormalities. Such data may also provide prognostic information concerning suitability for surgical intervention.

422 Noninvasive Myocardial Imaging With Potassium-43 and Rubidium-81 in Patients With Left Bundle Branch Block

RONALD L. McGOWAN, THOMAS G. WELCH, BARRY L. ZARET, ANDREW L. BRYSON, NEIL D. MARTIN and M. D. FLAMM

Left bundle branch block should be added to the conditions that can produce false positive myocardial images. Reduced radioactivity in the region of the interventricular septum similar to that observed in anteroseptal myocardial infarction was observed at rest in 25 of 27 subjects with left bundle branch block studied with noninvasive imaging. The image defect was less distinct or even normal with exercise in patients with no anatomic heart disease.

Continued on page A13

IN PREDICTABLE ANGINA*



...during the postprandial period

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.

Duration of Effect: One to two hours.

CHEWABLE SORBITRATE® 5 mg.
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UP TO 2 HOURS OF ANGINA PROTECTION. AT MEALTIME...AND ANY OTHER TIME OF STRESS.

STUART PHARMACEUTICALS | Wilmington, DE 19897
Division of ICI United States Inc.

CONTENTS

429 **Electrophysiologic Effects of Atropine on Human Sinus Node and Atrium**

RAMESH C. DHINGRA, FERNANDO AMAT-Y-LEON, CHRISTOPHER WYNDHAM, PABLO DENES, DELON WU, J. MAURICE POUGET and KENNETH M. ROSEN

Intravenous injection of 1 to 2 mg of atropine in 17 patients shortened sinus cycle length, sinus recovery time and calculated sinoatrial conduction time. Shortening of atrial refractory periods with atropine suggests that vagotonia prolongs atrial refractoriness in man.

435 **Reduction of S-T Segment Elevation With Infusion of Nitroprusside in Patients With Acute Myocardial Infarction**

NAJAM A. AWAN, RICHARD R. MILLER, ZAKAUDDIN VERA, ANTHONY N. DeMARIA, EZRA A. AMSTERDAM and DEAN T. MASON

The infusion of nitroprusside in 12 patients with an acute anterior myocardial infarction decreased myocardial ischemic injury as assessed by S-T mapping and reduced the myocardial oxygen consumption index of pressure-time per minute. The absence of any significant relation between these two variables suggests that nitroprusside may directly augment regional blood flow to ischemic myocardium.

METHODS

440 **Computer Detection of Premature Ventricular Complexes: A Modified Approach**

SUZANNE B. KNOEBEL, D. EUGENE LOVELACE, SUSAN RASMUSSEN and STEVEN E. WASH

This data reduction system for arrhythmia detection has a less than 2 percent false negative and 3 percent false positive rate of identification of premature ventricular complexes. The system increases the clinical utility of computer analysis and reduces post-computer processing time.

PEDIATRIC CARDIOLOGY

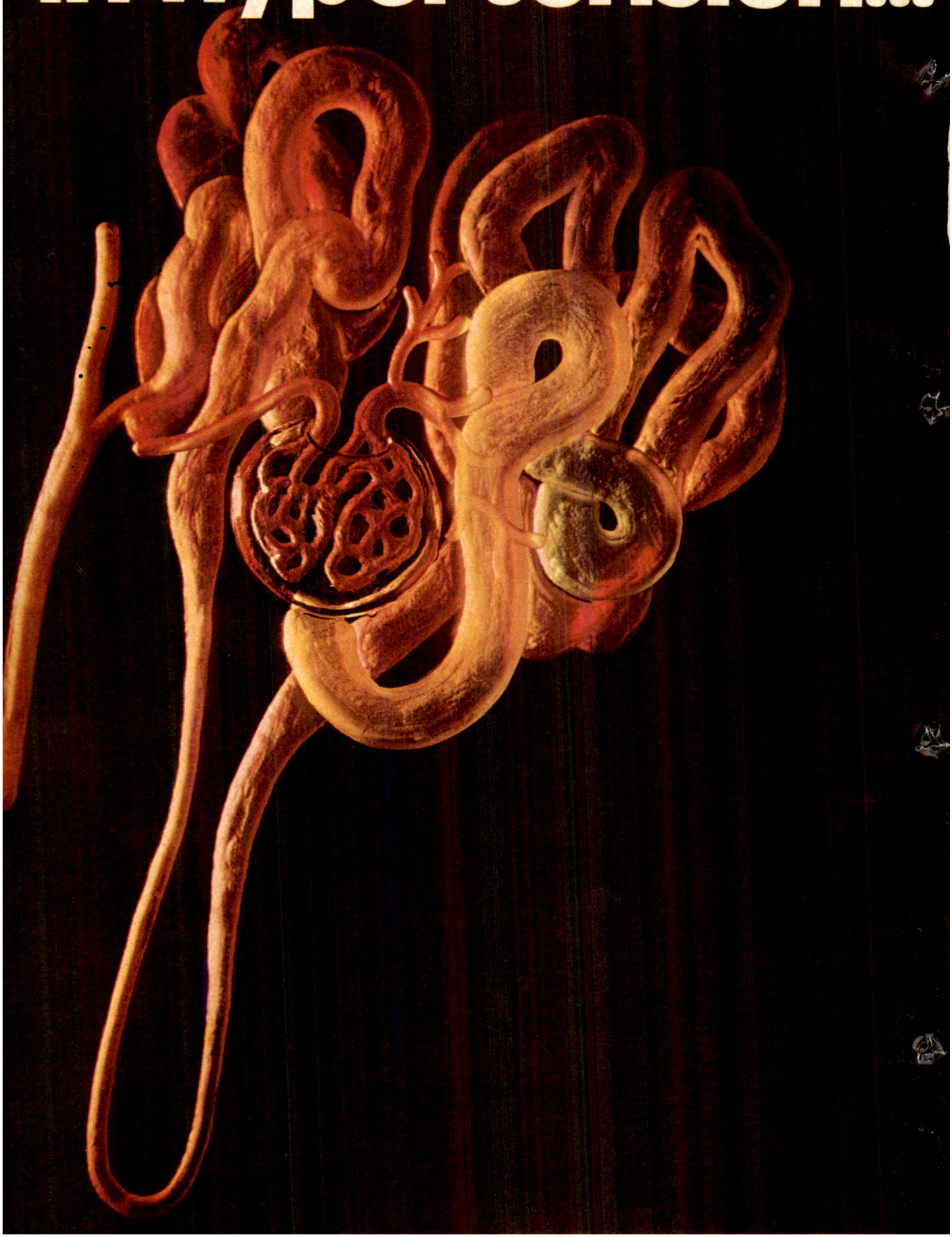
448 **Significance of Pacemaker Recovery Time After the Mustard Operation for Transposition of the Great Arteries**

GALAL M. EL-SAID, PAUL C. GILLETTE, CHARLES E. MULLINS, MICHAEL R. NIHILL and DAN G. McNAMARA

This study in 24 patients 6 months to 3 years after the Mustard operation for transposition of the great arteries shows that rhythm abnormalities were likely to develop in those with a prolonged pacemaker recovery time but that a normal recovery time did not exclude abnormal sinus nodal function.

Continued on page A17

In hypertension...



Hygroton® 50 mg.
(chlorthalidone)
blocks sodium retention longer

Diuretics reduce blood pressure by blocking sodium retention to lower "effective" volume. But the body's renal compensatory mechanisms are mobilized to promote a secondary sodium conservation, expand "effective" volume and perhaps reelevate blood pressure. Sustained control of "effective" volume is therefore essential to treatment. No other diuretic blocks sodium retention longer than Hygroton.

Provides sustained control

Since the effects of Hygroton are exerted over a 24-hour period, sodium diuresis is gradual and prolonged. At the renal tubular level, Hygroton thwarts attempts of the renin/angiotensin/aldosterone system to conserve sodium, thus keeping "effective" volume and blood pressure down. Inadequate doses of diuretics may permit the renin/angiotensin/aldosterone system to prevail, but Hygroton helps inhibit it through . . .
a "24-hour sentry" effect

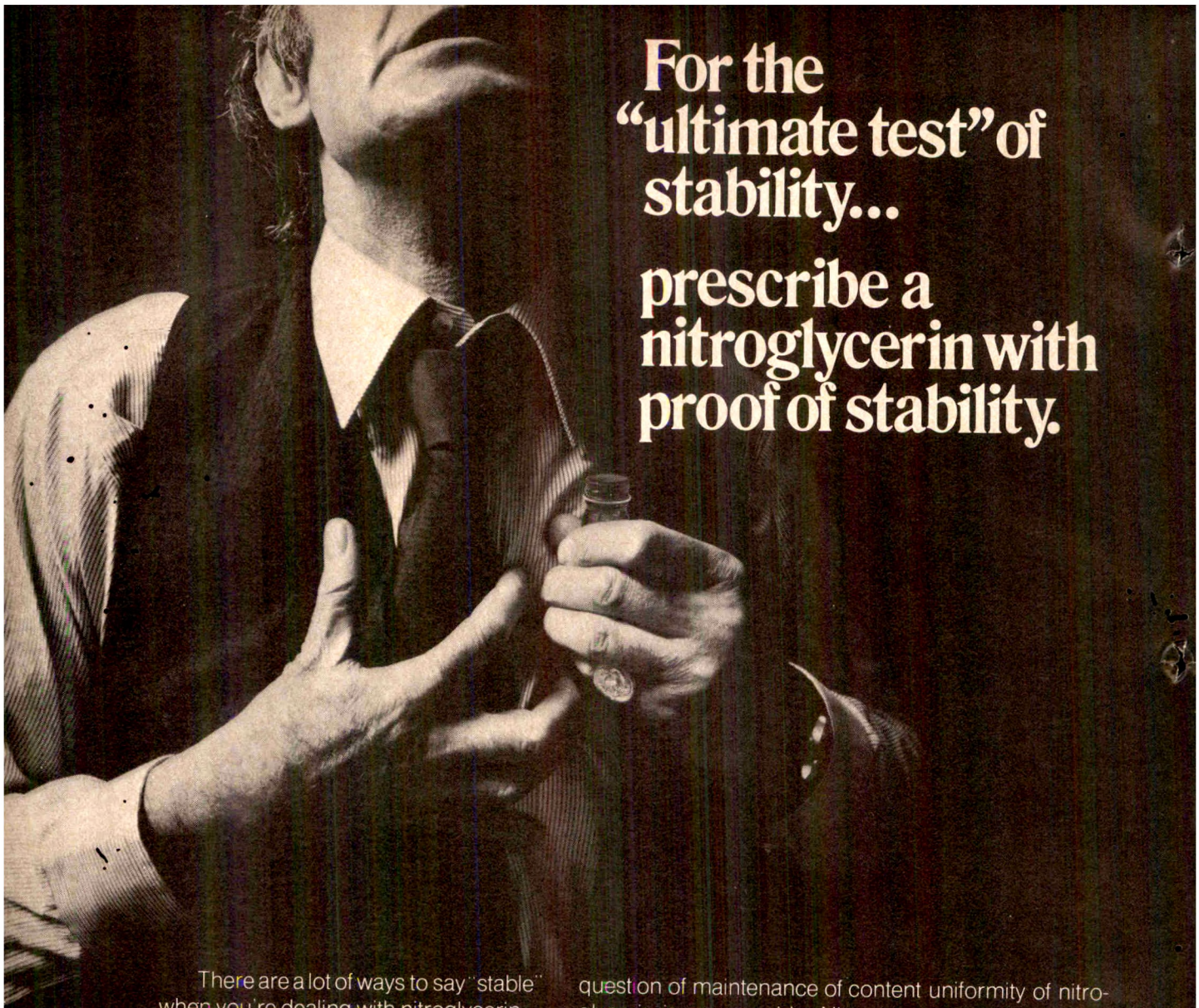
Enhances patient compliance

The "24-hour sentry" effect of Hygroton allows once-a-day administration. This uncomplicated regimen encourages patient compliance through simplicity and economy. Proven efficacy and compliance have made Hygroton one of the most widely prescribed diuretic/antihypertensives for mild to moderate hypertension today.

Hygroton®
the 24-hour sentry
For effective once-daily therapy

USV PHARMACEUTICALS
USV Pharmaceutical Mfg. Corp.
Manati, P.R. 00701

BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone; routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May be additive or potentiative of the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Usage in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in cord blood and breast milk. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.



For the "ultimate test" of stability...

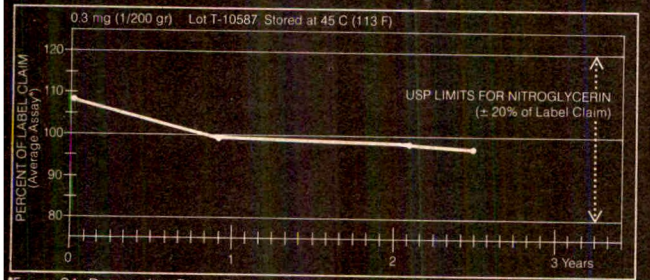
prescribe a nitroglycerin with proof of stability.

There are a lot of ways to say "stable" when you're dealing with nitroglycerin.

That's why the testing of Nitrostat *includes* tests to simulate, as closely as possible, the actual conditions of use.

For example, we test for **wickability**—a Parke-Davis test (the time in seconds required for water to wet the tablet completely by capillary action under controlled conditions) to simulate under-the-tongue conditions.

Heat-stable? Yes. Up to 45 C (113 F), considerably higher than "vest pocket" temperatures.



*Fusari SA: Data on file, Parke, Davis & Company, Detroit, Michigan. (Test results were similar for the 0.4-mg and the 0.6-mg strengths.)

Potency and Content Uniformity? The average assay still shows almost 100% of label claim more than 30 months after manufacture. What's more, the crucial question of maintenance of content uniformity of nitroglycerin is answered by Nitrostat as proved by assay: less chance of your patient taking a superpotent or, more important, a subpotent tablet.

Disintegration? We test it using the USP test in 800 ml of water. All tablets usually disintegrate within 30 seconds (USP limit = 2 minutes).

Dissolution? Using NF Method II, we show greater than 90% dissolution in 30 seconds.

Now, each factor taken by itself may not be decisive. But taken together, they add up to a good reason to prescribe Nitrostat.

Nitrostat®

sublingual tablets
stabilized formula

(nitroglycerin tablets, USP)

0.3 mg (1/200 gr)—0.4 mg (1/150 gr)—0.6 mg (1/100 gr)

Available in bottles of 100
and Convenience Packs of 25

PD-JA-1669-J-P(3-76)

PARKE-DAVIS PARKE, DAVIS & COMPANY, Detroit, Michigan 48232

CONTENTS

452 **Variation in the Size and Distensibility of the Pulmonary Arteries in *d*-Transposition of the Great Arteries**

KALIM UDDIN AZIZ, MAURICE A. NANTON, LANGFORD KIDD, CHARLES A. F. MOES and RICHARD D. ROWE

Cineangiograms of 117 patients with *d*-transposition of the great arteries showed that the pulmonary artery was largest in patients with ventricular septal defect or patent ductus arteriosus, or both, as a result of increased pulmonary arterial pressure and flow. Excessive distensibility of the main pulmonary artery and hypoplasia of the first branch pulmonary arteries allow greater accommodation of left ventricular stroke volume in the main pulmonary artery.

458 **Echocardiographic Abnormalities in Acute Rheumatic Fever**

RICHARD M. SCHIEKEN and RICHARD E. KERBER

Serial echocardiograms proved useful in assessing the severity of carditis in 12 children with acute rheumatic fever. In seven children with regurgitation and congestive heart failure the initial velocity of circumferential fiber shortening decreased, the velocity of circumferential fiber shortening increased to exceed the expected normal value and the left atrial dimension, greatly increased initially, remained large.

REPORTS ON THERAPY

463 **Surgical Treatment of Degenerative Mitral Regurgitation**

NEAL W. SALOMON, EDWARD B. STINSON, RANDALL B. GRIEPP and NORMAN E. SHUMWAY

The operative mortality for mitral valve replacement in 66 patients with myxomatous degeneration of the mitral valve was 6 percent. Preoperative variables with a significantly adverse effect on patient survival included patient age greater than 50 years, New York Heart Association functional class IV, left ventricular end-diastolic pressure greater than 12 mm Hg and mean pulmonary arterial wedge pressure greater than 16 mm Hg. Earlier operative intervention should be considered in patients with myxomatous mitral degeneration and mitral insufficiency before the advent of severe and possibly irreversible impairment of ventricular function.

469 **Hemodynamic Effects of Nitroglycerin Ointment in Congestive Heart Failure**

WILLIAM R. TAYLOR, JAMES S. FORRESTER, PETER MAGNUSSON, TERUO TAKANO, KANU CHATTERJEE and H. J. C. SWAN

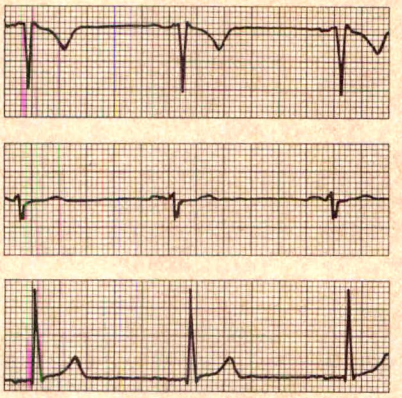
The following hemodynamic effects of nitroglycerin ointment, lasting 3 to 6 hours, in 10 patients with chronic congestive heart failure, indicate its potential value in treating congestive heart failure: Pulmonary capillary wedge pressure decreased, cardiac index increased, systemic and pulmonary vascular resistance decreased, venous capacitance increased, mean arterial pressure decreased and heart rate remained unchanged.

Continued on page A19

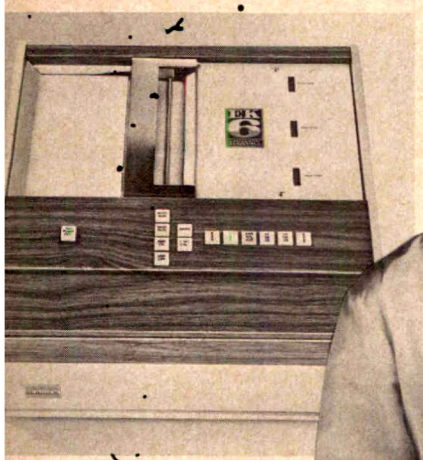
More diagnostic accuracy: three views of every heartbeat, simultaneously.

Burdick EK-6 3-channel electrocardiograph—ing periods of cardiac instability, more accurate gnosis demands more complete data. Having that rmation in seconds is one reason you should have new Burdick EK-6 3-channel electrocardiograph.

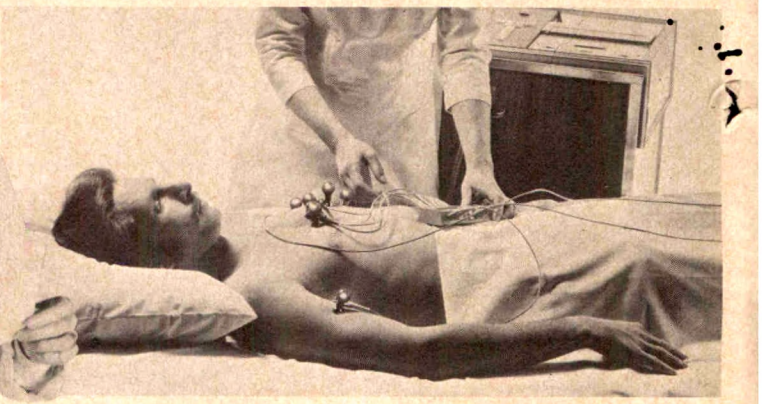
EK-6 gives you three different perspectives of the rt all at once. You can perceive the status of the rt more accurately, with recording flexibility that is cal for complete cardiac diagnosis.



Direct-recording accuracy—Burdick's heated stylus, heat-sensitive paper and flat writing surface combine to produce tracings of uncommon clarity and accuracy. And the EK-6 produces a higher fidelity in the ECG to eliminate distortions or errors common with inferior recordings.







nplete 12-lead ECGs in seconds—Once the trodes are attached, ning a single AUTO N button automatically pro- es a complete 12-lead ECG ly for mounting. Three-lead ups are automatically iden- d and marked. Lead gths, selection, standardiz- ns, sensitivity settings, er speed, and lead check also automatically con- ed. Or the EK-6 may be grammed for manual or i-automatic operation.

Fast, sure electrode placement—Tangled leads and complicated lead replacement are nearly eliminated. The Burdick EK-6 features color-coded, variable-length lead wires that allow the operator to place the leads quickly and securely. Burdick's unique patient-cable junction block will accept 10 individual leads for standard ECGs, or fifteen when XYZ (Frank) leads are desired. Also, our patient cable is easily repairable.

You can view your patient's heart from three perspectives at one time with the Burdick EK-6 3-channel electrocardiograph. For a demonstration or more information, call, toll-free, (800) 356-0701. Within Wisconsin: (608) 868-7631. Or write The Burdick Corporation, Milton, Wisconsin 53563

BURDICK

CONTENTS

474 **Nitroglycerin Ointment in Acute Myocardial Infarction**

PAUL W. ARMSTRONG, M. THOMAS MATHEW, KAYOOMARS BOROOMAND and JOHN O. PARKER

After application of nitroglycerin ointment in 22 patients with acute myocardial infarction, peak decrements were observed in their mean arterial pressure, pulmonary capillary wedge pressure, right atrial pressure and heart rate × systolic blood pressure. Total peripheral resistance also decreased. These data showed that nitroglycerin ointment improved cardiac performance while reducing the determinants of myocardial oxygen consumption and preserving the transmyocardial gradient for coronary blood flow.

REVIEWS

479 **Medical Versus Surgical Treatment of Unstable Angina**

HERBERT N. HULTGREN

This review examines critical problems in the evaluation of treatment methods for unstable angina and presents a summary evaluation of five comparative studies. During a mean follow-up time of 18 months mortality rates of 13.8 and 7.1 percent and incidence rates of nonfatal myocardial infarction of 12 and 18.2 percent, respectively, were found in 280 medically treated patients and 334 surgically treated patients. Further data from large scale studies are necessary to evaluate the comparative mortality and morbidity in identifiable subgroups in which the risk of medical treatment alone may be greater than that of surgical treatment.

487 **The Heart in the Hurler Syndrome. Gross, Histologic and Ultrastructural Observations in Five Necropsy Cases**

VICENTE G. RENTERÍA, VICTOR J. FERRANS and WILLIAM C. ROBERTS

At necropsy, characteristic Hurler cells were found in the coronary arteries, four cardiac valves, mural endocardium, myocardial walls and aorta of five subjects with the Hurler syndrome. In addition, granular cells were observed in the coronary arteries, atrioventricular valves and in the myocardial interstitium. These latter cells, producing collagen in an abnormal way, are probably responsible for the heavy deposits of collagen in the cardiovascular system of these patients.

DIAGNOSTIC SHELF

502 **Echocardiographic Evaluation of Tricuspid Valve Endocarditis. An M Mode and Two Dimensional Study**

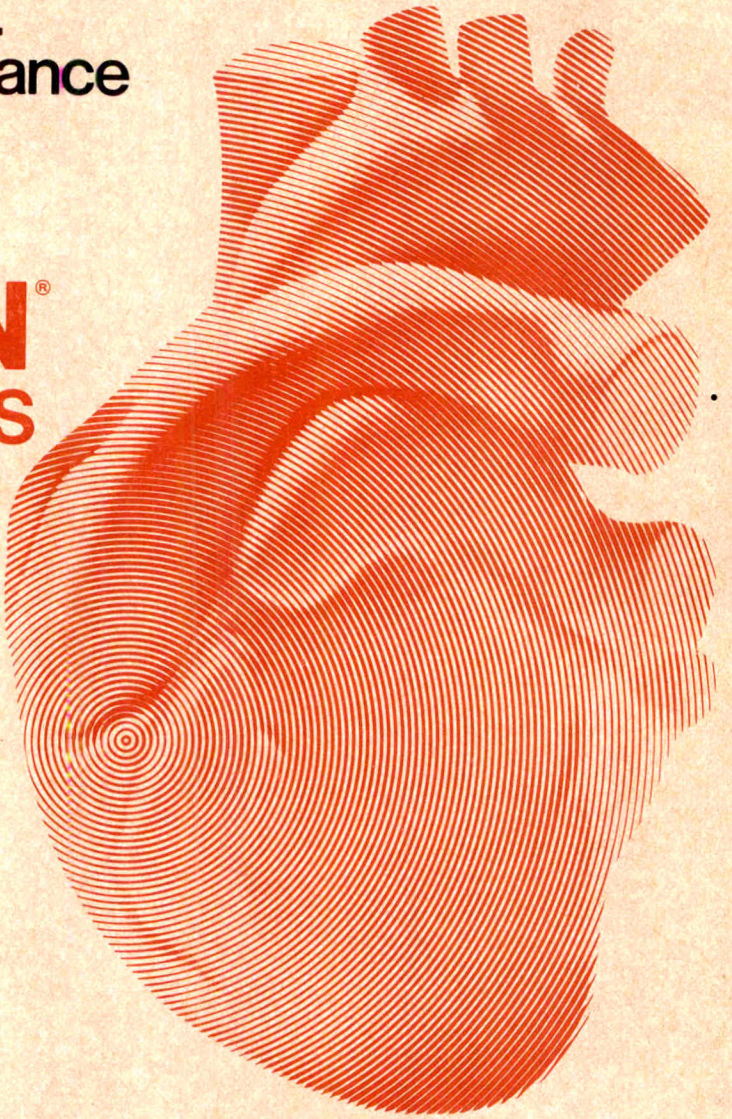
JOSEPH KISSLO, OLAF T. VON RAMM, ROBYN HANEY, ROBERT JONES, S. STANLEY JUK and VICTOR S. BEHAR

Standard M mode echocardiography and a new real time two dimensional echocardiographic imaging system accurately followed and assessed the progressive anatomic destruction and functional deterioration of the tricuspid valve in a patient with bacterial endocarditis.

Continued on page A21

The Pacekeeper™

For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance



CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance
- ☐ Full quinidine cardiodynamics
- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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CONTENTS

CASE REPORTS

508 Pathologic Correlations in Three Cases of Bilateral Bundle Branch Disease With Unusual Electrophysiologic Manifestations in Two Cases

SAROJA BHARATI, MAURICE LEV, RAMESH DHINGRA, DELON WU, JOSE ARUGUETE, JUAN MIR and KENNETH M. ROSEN

Excellent correlation between electrophysiologic and pathologic data in three cases of intraventricular conduction disease demonstrated an anatomic basis for the electrophysiologic findings resembling bilateral bundle branch block. Sinus nodal reentrance may be related to disease in the approaches to the sinoatrial node. The anatomic substrate for left axis deviation may be the greater involvement of the anterior portion than of the posterior portion of the main left bundle.

519 Quinidine-Induced Ventricular Flutter and Fibrillation Without Digitalis Therapy

RUDOLPH W. KOSTER and HEIN J. J. WELLENS

Moderate doses of quinidine first greatly prolonged the Q-T interval and later caused ventricular flutter and fibrillation in three patients. Such ventricular tachyarrhythmias during quinidine-associated syncope may possibly have the same electrophysiologic basis as ventricular fibrillation in patients with the Q-T prolongation syndrome.

524 Mustard Operation and Creation of Ventricular Septal Defect in Two Patients With Transposition of the Great Arteries, Intact Ventricular Septum and Pulmonary Vascular Disease

JAROSLAV STARK, MARC R. de LEVAL and JAMES F. N. TAYLOR

As demonstrated in two children with transposition of the great arteries, intact ventricular septum and severely increased pulmonary vascular resistance, application of the "palliative Mustard" procedure (correction of inflow by the Mustard technique and creation of a ventricular septal defect) accomplished useful palliation in subjects with this congenital heart condition by increasing systemic saturation and improving exercise tolerance and general health.

528 Cardiac Involvement in the Kugelberg-Welander Syndrome

HIROMITSU TANAKA, NOBUHIRO UEMURA, YOSHIFUMI TOYAMA, AKIO KUDO, YOHSUKE OHKATSU and TAKUYA KANEHISA

Two patients with the Kugelberg-Welander syndrome (juvenile form of progressive spinal muscular dystrophy) associated with cardiomyopathy and cardiomegaly highlight the need to document and study the cardiac changes in the heredofamilial degenerative diseases, including those in which the association with cardiomyopathy is considered uncommon. One patient had atrial flutter with complete atrioventricular block due to A-H block; the other had slight interstitial fibrosis of the myocardium on myocardial biopsy.

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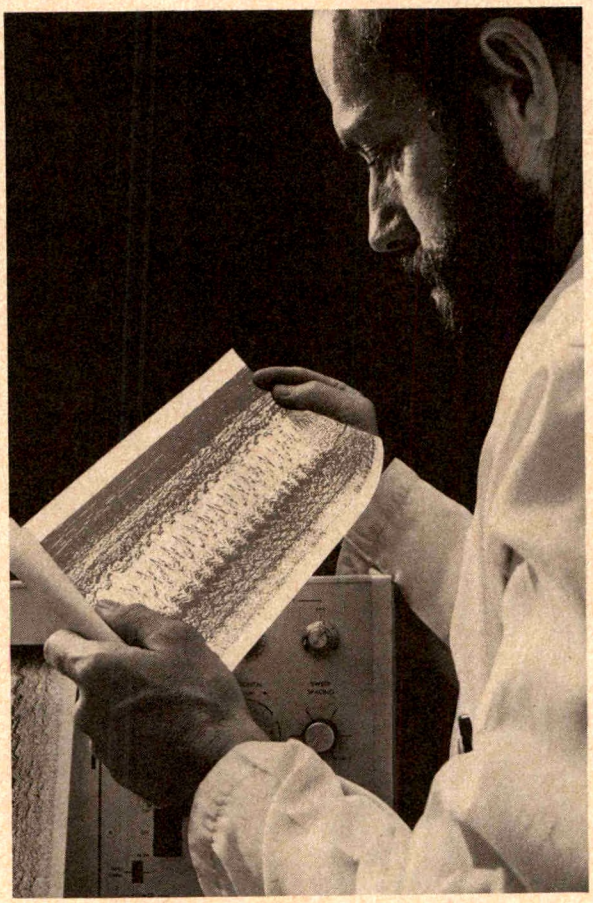
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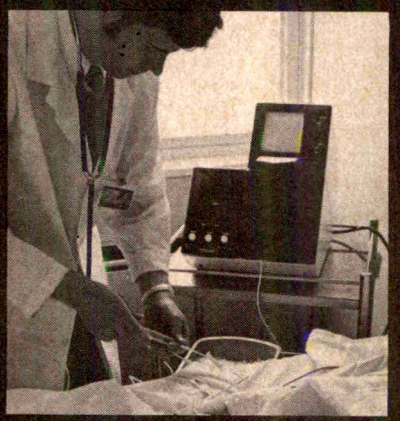
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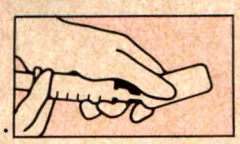
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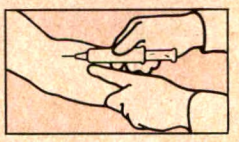
HYPERSTAT I.V. supplied as a 20 ml ampule containing 300 mg diazoxide in ready to use solution.

*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J* 87(6): 791-795; June 1974.

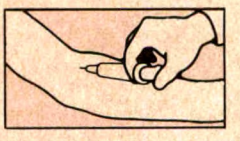
Administration guidelines



1. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml ampule contains 300 mg diazoxide).



2. Hospitalized patient should be recumbent. Insert needle only into a peripheral vein.



3. Inject entire dose I.V. in 30 seconds or less. Remove needle carefully—avoid extravasation.

4. Keep patient recumbent for at least half an hour after injection; monitor BP closely until stabilized—usually 15-30 minutes.

5. If patient is to be ambulatory, measure BP in standing position before ending surveillance.

6. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective (generally within a few days).

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information, a summary of which appears on the facing page.

HYPERSTAT® I.V. (brand of diazoxide, USP) Injection

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

INDICATIONS For the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled. HYPERSTAT I.V. Injection is ineffective against hypertension due to pheochromocytoma.

CONTRAINDICATIONS It should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt, or in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

WARNINGS Safety in pregnancy and in children has not yet been established. Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults. Hypotension may occasionally result. If severe enough to require therapy, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine. Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored, especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide. Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. Concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions). Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent. Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available. It should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively. Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response. As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental. Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection. Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by unconsciousness, convulsions, paralysis, confusion or focal neurological deficit, such as numbness of the hands; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported. Papilledema, induced by plasma volume expansion secondary to the administration of diazoxide, was reported in one patient who had received eleven injections over a twenty-two day period.

Other adverse reactions: Vasodilative phenomena, such as orthostatic hypotension, sweating, flushing, and generalized or localized sensations of warmth; supraventricular tachycardia and palpitation; bradycardia; various transient neurological findings secondary to alterations in regional blood flow to the brain, such as headache (sometimes throbbing), dizziness, lightheadedness, sleepiness (also reported as lethargy, somnolence or drowsiness), euphoria or "funny feeling", ringing in the ears and momentary hearing loss, and weakness of short duration; chest discomfort or nonanginal "tightness in the chest"; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; and various respiratory and gastrointestinal findings, secondary to the relaxation of smooth muscle, such as dyspnea, cough and choking sensation; nausea and vomiting and/or abdominal discomfort, anorexia, alteration in taste, parotid swelling, salivation, dry mouth, lacrimation, ileus, constipation and diarrhea. Also, warmth or pain along the injected vein; cellulitus without sloughing and/or phlebitis at the site of extravasation; back pain; and increased nocturia. Apprehension or anxiety, malaise and blurred vision occurred on single occasions.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia. Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

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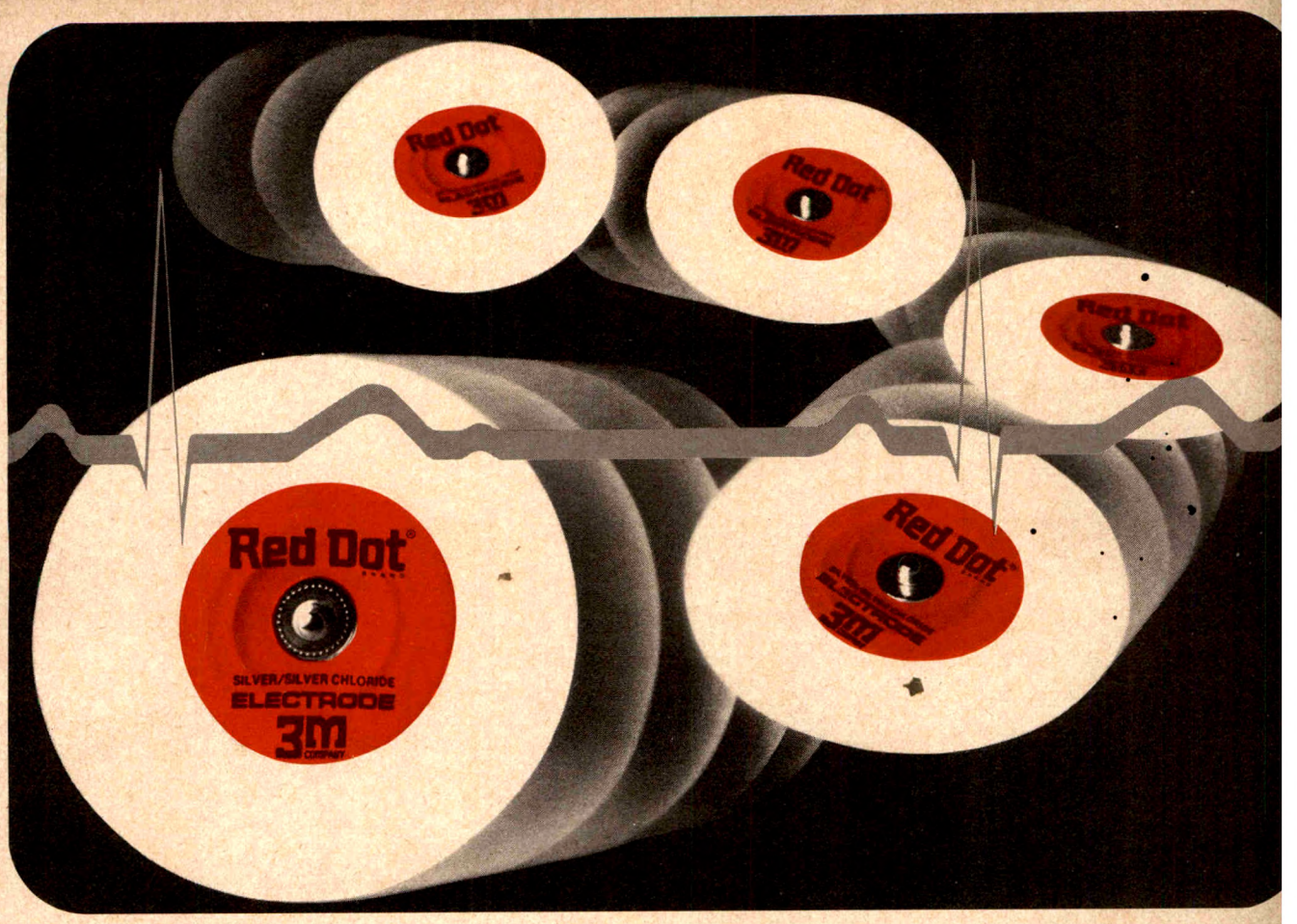
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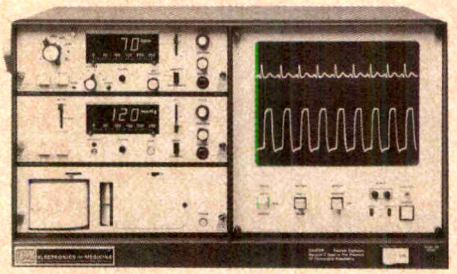
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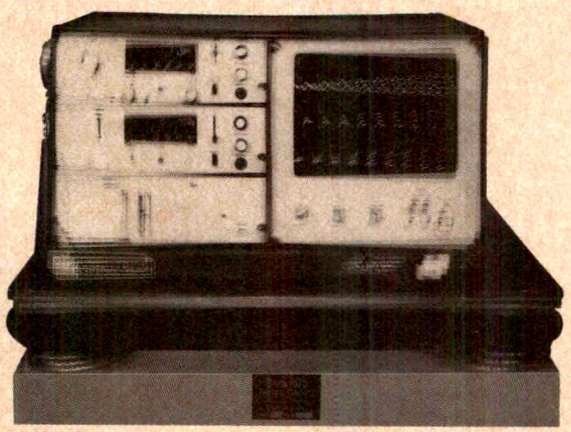
We make patient monitoring systems second to none. Systems with non-fade displays and split-screen holds. With our monitors you can freeze traces on half the screen while continuing to view the patient's current condition on the other half. Very valuable instruments. And competitively priced.

But that's only part of the story. Because we design E for M monitoring systems for dependability, we know how each component should be tested. And so, we test and re-test each completed unit. And torture test it. And then put it through a continuous-use test of more than four days. Because we do all of this, we know our monitors will last. That's why we can offer the longest warranty available in patient monitoring today.

Plus 10 years of guaranteed protection.

But, that's not all. Starting now, when you buy an E for M Patient Monitor, you'll also get protection for 10 long years. If, tomorrow...or any time in the next 10 years...we can't provide parts and service for the E for M monitor you buy today, you can trade it in for its replacement model, with an allowance based on age of up to 100% of the original price!

Performance plus great dependability. And warranty protection that's every bit as good as our patient monitors. That's what you'll get from us when you call with your requirements.



The torture test shakes everything up to make sure nothing shakes loose.

E FOR M

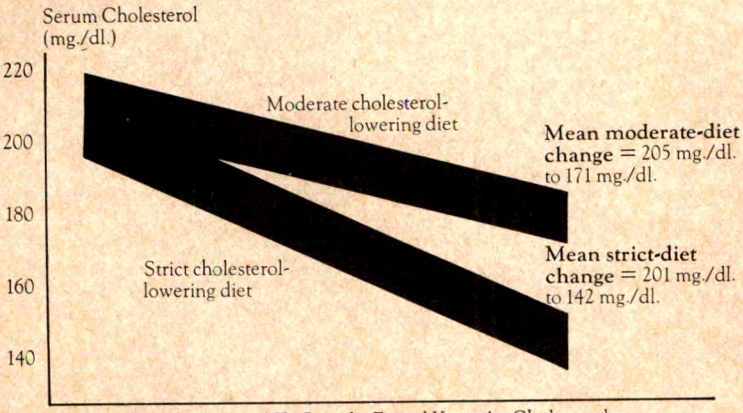
ELECTRONICS FOR MEDICINE, INC.

30 Virginia Road,
White Plains, N.Y. 10603
(914) 946-1187

When elevated cholesterol calls for decreased saturates...

Mazola helps.

Helps lower serum cholesterol



Adapted from Anderson, J.T., Grande, F., and Keys, A.: Cholesterol-lowering diets, J. Am. Diet. Assoc., 62:133, 1973.

In this study, a standard diet was modified to produce a moderate cholesterol-lowering diet, using skim milk, lean meats, fish, two eggs per week, poultry, and *Mazola*® corn and corn oil margarine. The average decrease in serum cholesterol for the 12 subjects was 17%. Serum cholesterol was reduced even more (average of 29% for 36 subjects) when a strict diet was used, which excluded butterfat and margarine, further reduced meat and eggs, and allowed *Mazola* corn oil as the only visible fat. All changes were considered highly significant.

Mazola corn oil and margarine help diet adherence

For cholesterol control, long-term adherence is essential. To gain patient acceptance, the polyunsaturated fats used must pass the test of taste. For flavor and lightness, *Mazola* corn oil and margarine qualify.

Helps patients live with the diet

Send coupon for your Mazola resources file

A professional file of 11 patient and physician aids for reduction of risk in atherosclerosis and coronary heart disease is now available free upon request. Just mail this coupon to Dr. D.M. Rathmann, *Mazola* Nutrition Information Service, Best Foods, a Division of CPC International Inc., Department MH, Box 307, Coventry, Ct. 06238.
Included are:

Patient Aids...*Mazola* helps your patients live with a cholesterol-control diet with (1) "A Diet for Today"—practical menus and recipes for cholesterol control. (2) "Beyond Diet...Exercise Your Way to Fitness and Heart Health." (3) "Q & A, Fats and Oils."



Mazola®
Corn Oil & Margarine

Physician Aids...*Mazola* helps you evaluate and educate the high-risk patient with (1) "Coronary Risk Handbook." (2) Pad of coronary risk assessment and management forms. (3) Desk pad of heart anatomy. (4) "Atherosclerosis"—80-page physician education monograph with film order form (5) "Learn...before it's too late"—52-page nutrition learning system for patients with film order form. (6) Reprint of "Cholesterol lowering diets: Experimental trials and literature review." (7) "Nutritive Values of Food Products Made by Best Foods." (8) "A Note to Professionals about 'A Diet for Toda

NUTRITION INFORMATION SERVICE Mazola ™

Dr. _____
Name

Street Address

City *State* *Zip Code*

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BFF

In Refractory Congestive Failure Associated with Hypotension or Shock

INTROPIN®
(dopamine HCl)

Provides Patients with a Third Dimension of Therapy



Intropin: a logical addition for hospitalized patients refractory to digitalis and diuretics

When cardiac output is insufficient, or when renal blood flow and urine output do not respond in spite of therapy, a new dimension should be considered as an adjunct to the standard digitalis/diuretic regimen.

Intropin (at recommended doses) may potentiate digitalis/diuretic therapy in two ways. First, Intropin exerts a positive inotropic effect which can result in greater cardiac output, increased renal blood flow and diuresis. In addition, Intropin directly stimulates "dopaminergic" receptors in the kidney to cause renal dilation, increased urine flow and sodium excretion.

Thus, Intropin works both indirectly and directly on the renal vascular beds to decrease accumulated fluids.

Pharmacologic guidelines for adding Intropin to the treatment of patients refractory to digitalis/diuretic therapy

	Cardiac Output	Renal Blood Flow	Urine Flow	Sodium Excretion
DIGITALIS	no change to increase ↑	increase only if cardiac output increases (no direct effect) ↑	increase only if renal blood flow increases ↑	increase only if renal blood flow increases ↑
DIURETICS	no effect	no effect	increase due to increased sodium excretion ↑	increase (direct effect) ↑
INTROPIN®	increase above 5 mcg/kg/min ↑	increase 2-30 mcg/kg/min ↑	increase 2-30 mcg/kg/min ↑	increase if renal blood flow increases 2-30 mcg/kg/min ↑

This chart graphically demonstrates:

1. the effects of digitalis on renal blood flow, urine output and sodium excretion are primarily related to cardiac output;
2. diuretics, while favorably affecting urine flow and sodium excretion, do not influence cardiac output or renal blood flow;
3. Intropin favorably affects cardiac output at doses above 5 mcg/kg/min and increases renal blood flow, urine output and sodium excretion at doses of 2 to 30 mcg/kg/min, regardless of the effect of the drug on cardiac output.

Intropin: a catecholamine with unique actions

Intropin is a unique catecholamine that increases cardiac output, vital organ perfusion and urine output without increasing the likelihood of serious side effects. With Intropin, the myocardial oxygen supply/demand ratio appears to remain stable.

Concurrent administration of Intropin and diuretic agents may produce an additive or potentiating effect.

As with most drugs administered in serious situations, a key to favorable prognosis is the initiation of Intropin as soon as practical after the onset of unfavorable signs. Patients most likely to respond are those whose myocardial function, urine output and blood pressure have not undergone profound deterioration.

Intropin: points about dosage

Before administering Intropin, the physician should be familiar with the effects of the drug at various dosage levels (see chart) and should especially note the paradoxical results of Intropin at ranges of over 30 mcg/kg/min - increases in systemic vascular resistance plus a decrease in renal blood flow and urine output. These norepinephrine-like phenomena can be reversed, if desired, by reducing the dose.

Intropin is compatible with digitalis and diuretics employed in the treatment of refractory congestive heart failure.

Intropin must be diluted in a suitable intravenous solution and given by I.V. drip under close medical supervision.

The half-life of Intropin is somewhat less than 2 minutes, and all effects of the drug usually dissipate within 10 minutes after cessation of the medication.

The effects of Intropin at various dose levels

	2-5 mcg/kg/min	5-30 mcg/kg/min	over 30 mcg/kg/min
Cardiac Output	no change	increase	increase
Stroke Volume	no change	increase	increase
Heart Rate	no change	there is an initial increase followed by a decrease toward normal rate as infusion continues	
Myocardial Contractility	no change	increase	increase
Potential for Excessive Myocardial Oxygen Demands	low* coronary blood flow increased	low* coronary blood flow increased	data unavailable
Potential for Tachyarrhythmias	low*	low*	moderate
Total Systemic Vascular Resistance	slight decrease to no change	no change to slight increase	increase
Renal Blood Flow	increase	increase	decrease
Urine Output	increase	increase	decrease

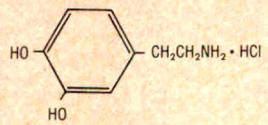
*Low but needs monitoring

See the following page for full prescribing information.

INTROPIN®
(dopamine HCl)

INTROPIN® (dopamine HCl)
5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs — Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output — Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension — Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy — Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children — The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia — Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure — If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation — INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease — Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT — Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics — Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required — Close monitoring of the following indices — urine flow, cardiac output and blood pressure — during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution — Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration — INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Adminstration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

ARNAR-STONE LABORATORIES, INC.
Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation

Printed in U.S.A.

ASL-09-76-934



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TEKTRONIX Portable Patient Monitors give you unmatched value

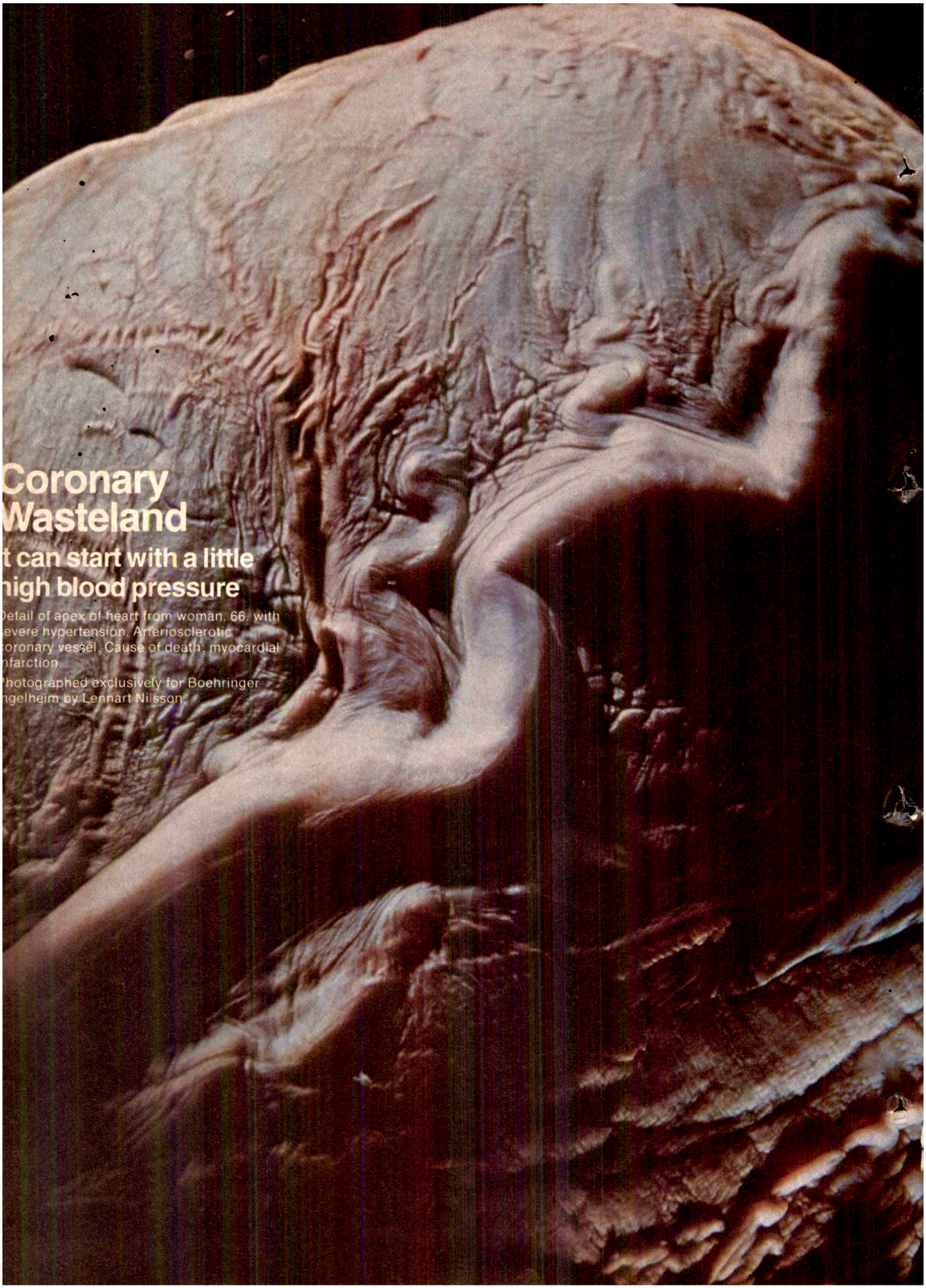
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Performance capability—only Tektronix gives you a line of portable patient monitors that includes in a monolithic package: single or dual pressure . . . analog display with or without digital readout . . . optional hard copy of analog and alphanumerics such as elapsed time, patient temperature, heart rate, systolic/diastolic and mean pressure . . . and much more! **Portability**—all monitors are only 9 x 11½ x 6 inches and 12 pounds (with recorder 9 x 11½ x 9½ inches and 18 pounds). **Easy operation**—color-coded control panels, pushbutton functions and a clear, bright display make TEKTRONIX Monitors simple to use. **Reliability and back-up service**—even though their accuracy and dependability are excellent, 35 Tektronix Service Centers nationwide provide 24-hour turn-around repair if needed.

Really compare CALL TOLL FREE 800 547-4804

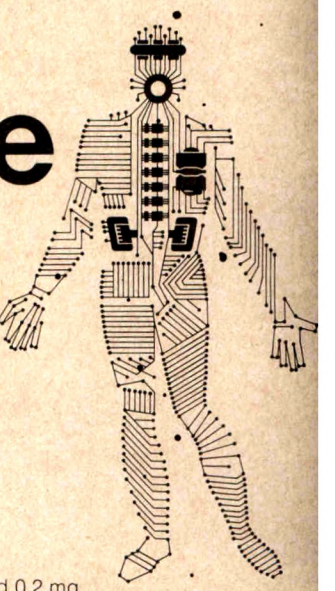
Portable Patient Monitors
In a Class by Themselves

TEKTRONIX®


Coronary
Wasteland
t can start with a little
high blood pressure
Detail of apex of heart from woman, 66, with
severe hypertension. Arteriosclerotic
coronary vessel. Cause of death: myocardial
infarction.
Photographed exclusively for Boehringer
Ingelheim by Lennart Nilsson.



Reach for normal blood pressure



In mild to moderate hypertension

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Catapres can make a diuretic look good.

When more than a diuretic is needed, adding Catapres usually lowers blood pressure more.[1]

You can add Catapres to Catapres to get pressure down near normal.

Wide therapeutic dosage range—0.2 mg to 2.4 mg* daily. Catapres may be all you need to reach near-normal levels.

*Doses as high as this have rarely been employed.

Catapres usually doesn't add a lot of problems.

The most common side effects—dry mouth, drowsiness, sedation—generally tend to diminish with time. When stopping Catapres, reduce dosage gradually over two to four days to avoid a possible rapid rise in pressure.

Please see next page of advertisement for a brief summary of the prescribing information including precautions, warnings, and adverse reactions.



Hypertension through the lens of Lennart Nilsson. The photographic genius of Lennart Nilsson has revealed extraordinary details of the human organism. Now, Boehringer Ingelheim has commissioned an exclusive series of photographs by Nilsson depicting hypertensive damage. This series, presented in the interest of continuing medical education, vividly records the progression of an insidious disease.

In mild to moderate hypertension

The Catapres Potential: blood pressure not just down, but down near normal

Catapres® Tablets of 0.1 and 0.2 mg (clonidine HCl)

Start with Catapres when a diuretic is wrong for your patient

Add Catapres when a diuretic alone doesn't let you reach near-normal pressure

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

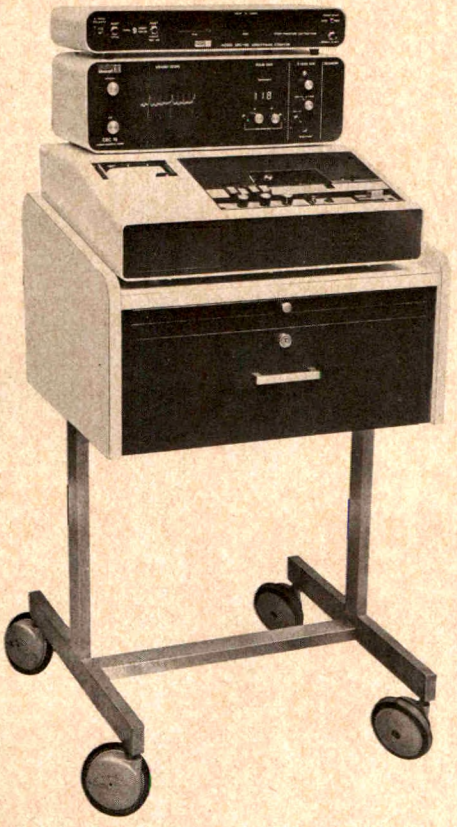
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CDC 70

The most versatile cardiac diagnostic unit!



Holter Monitor-Scanner; Stress testing; Resting ECG

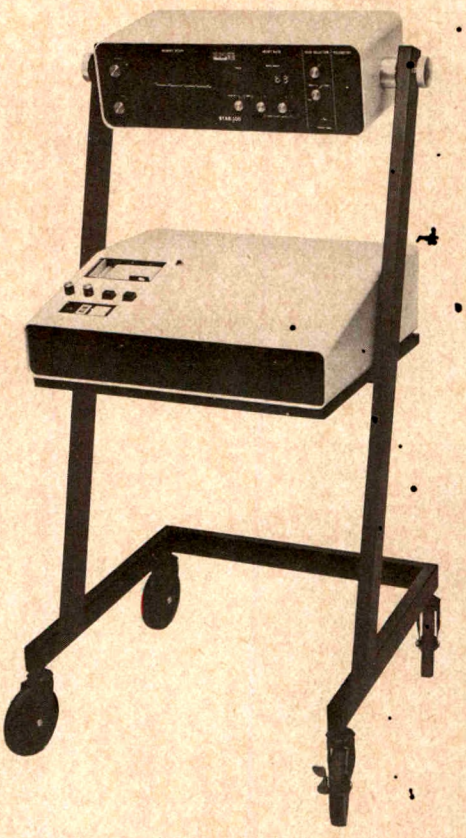
The only single instrument that allows total system utilization in these important cardiac diagnostic functions in office, clinic or hospital.

NEW ARC 150 Arrhythmia Counter option provides accurate quantitative data from your Holter tapes. It provides hourly and total counts of QRS, PVC and other ectopic beats at scan speeds.

Full 12 lead capability for resting ECG and stress testing with universal compatibility to interface with existing computer technology. Innovative design and solid state circuitry give you a most reliable system to suit your needs.

STAR 100

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LITHIUM
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Intermedics' Lithium Pacemaker System has the competition playing catch-up.

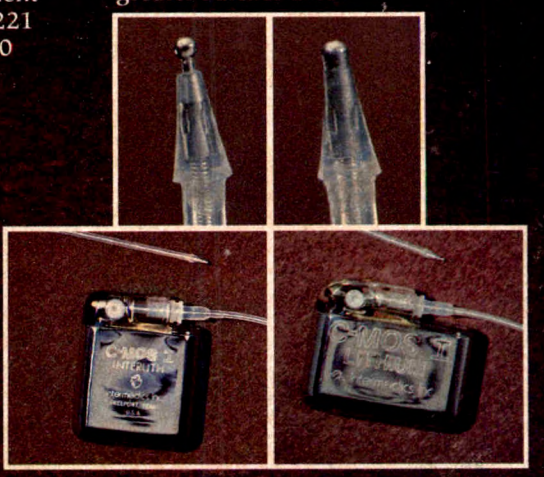
Intermedics, by combining the talents of experienced and aggressive designers, engineers, marketers and consulting physicians, has produced a complete pacemaker system so superior in design and performance that even the industry's giants are taking a second look at their products.

System Part 1:
The Pulse Generators

Intermedics' lithium pulse generators provide proven long-term, trouble-free operation and the low power consumption of C-MOS I circuitry combined with the superior life expectancy of a lithium battery hermetically sealed in its own container. Each pulse generator is also hermetically sealed in its own tissue-compatible, interference-resistant 316L stainless steel container, which features smoothly rounded edges for greatest patient comfort. Intermedics offers two excellent models: the original Model 221 *C-MOS I Lithium* weighing 90 grams (6.3 cm by 3.8 cm by 1.8 cm); and the new Model 223 *Interlith*™, weighing just 65 grams (5.5 cm by 4.2 cm by 1.4 cm). Both are available in demand or continual modes, with assured power life expectancies in excess of 6 years. Pre-set stimulation rates are available from 60 to 100 pulses per minute.

System Part 2: The Leads

Intermedics' pulse generators are designed to accept most competitors' leads. However, Intermedics manufactures a series of non-corroding, platinum-tipped leads which provide low stimulating and sensing thresholds and are designed in every way to increase the power life expectancy of Intermedics' pulse generators. Closed coil construction resists dislodgment and prevents lead fractures. Model 461 features a cylindrical tip, and the newer Model 463 offers a spherical tip for greater surface area.



System Part 3: Trace-A-Pace™ Remote Monitoring

Intermedics is the only pacemaker manufacturer on the market which provides a remote monitoring service at no additional charge with each implanted pulse generator. At the request of the patient's physician, the patient is provided with a lightweight, easy-to-use, portable transmitter. At any time, from any telephone, he can transmit his pulse and pacer rhythm to Intermedics. He simply attaches color-coded, dry electrodes, dials a toll-free telephone number, and places the telephone receiver on his transmitter. Intermedics will receive and record the rhythm strip and pulse generator rate. If any irregularity is observed, the patient's physician will be contacted immediately. With each transmission, the physician will receive a report and a copy of the rhythm strip, greatly reducing the time required for patient follow-up, and increasing the patient's confidence and mobility.

System Part 4:
Your Intermedics Representative

All Intermedics representatives are on call 24 hours a day. When necessary, they can have any Intermedics component or an entire Intermedics Lithium Pacemaker System in your hands shortly after you call.

For the location of your nearest Intermedics representative or additional information about our products, call toll-free 800-231-2330. In Texas call collect 713-233-8611.

Intermedics Inc.

P. O. Box 617 Freeport, Texas 77541

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Hypertension

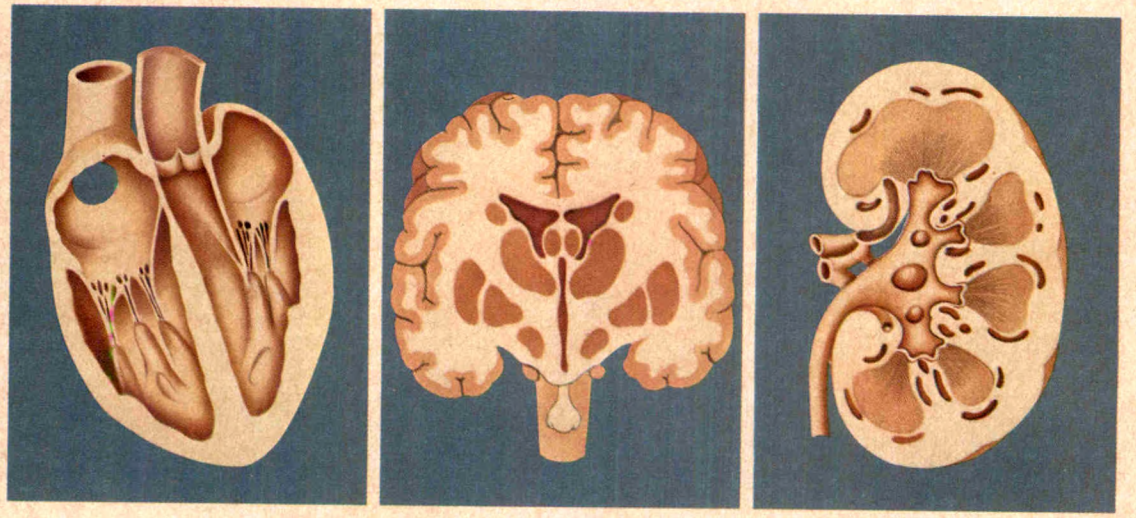
An important new indication for

Inderal®

Brand of

propranolol hydrochloride

Tablets 10 mg, 40 mg, 80 mg



Hypertension: a new indication for Inderal

Inderal (propranolol hydrochloride) is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. Inderal is not indicated for treatment of hypertensive emergencies.

Actions of Inderal

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

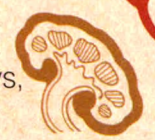
Mechanism of antihypertensive effects

The mechanism of the antihypertensive effects of Inderal has not been established. Among the factors that may be involved are:

(1) decreased cardiac output,



(2) inhibition of renin release by the kidneys, and



(3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.



Inderal dosage must be individualized

■ The initial dose is 80 mg Inderal daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved.

■ The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required.

■ The time course of full blood pressure response is variable and may range from a few days to several weeks.

■ Inderal is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When Inderal is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

How Inderal is supplied

TABLETS

—Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. (See HOW SUPPLIED section information on following pages.)



Before prescribing Inderal for hypertension, please read the full prescribing information on the following two pages.

Ayerst

(For full product information, see package circular.)

INDERAL®
Brand of propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Additional carcinogenicity studies in rats and mice conforming to recently accepted protocols are nearing completion and no drug-related increase in tumors has been observed.

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS

Hypertension

INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis

The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL (propranolol hydrochloride) exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL (propranolol hydrochloride) may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depress-

ing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL (propranolol hydrochloride) therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM *(e.g.,* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL (propranolol hydrochloride) may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects (fetal resorptions) have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

HYPERTENSION—*Dosage must be individualized.*

The initial dose is 80 mg INDERAL daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved. The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required. The time course of full blood pressure response is variable and may range from a few days to several weeks. INDERAL is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When INDERAL is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

ANGINA PECTORIS—*Dosage must be individualized.*

Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA — *Preoperatively* —60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

(propranolol hydrochloride)

TABLETS

—Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0461-81) and 1,000 (NDC 0046-0461-91). Also in unit dose package of 100 (NDC 0046-0461-99).

—Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0464-81) and 1,000 (NDC 0046-0464-91). Also in unit dose package of 100 (NDC 0046-0464-99).

—Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0468-81) and 1,000 (NDC 0046-0468-91). Also in unit dose package of 100 (NDC 0046-0468-99).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

Ayerst®

AYERST LABORATORIES
New York, N.Y. 10017

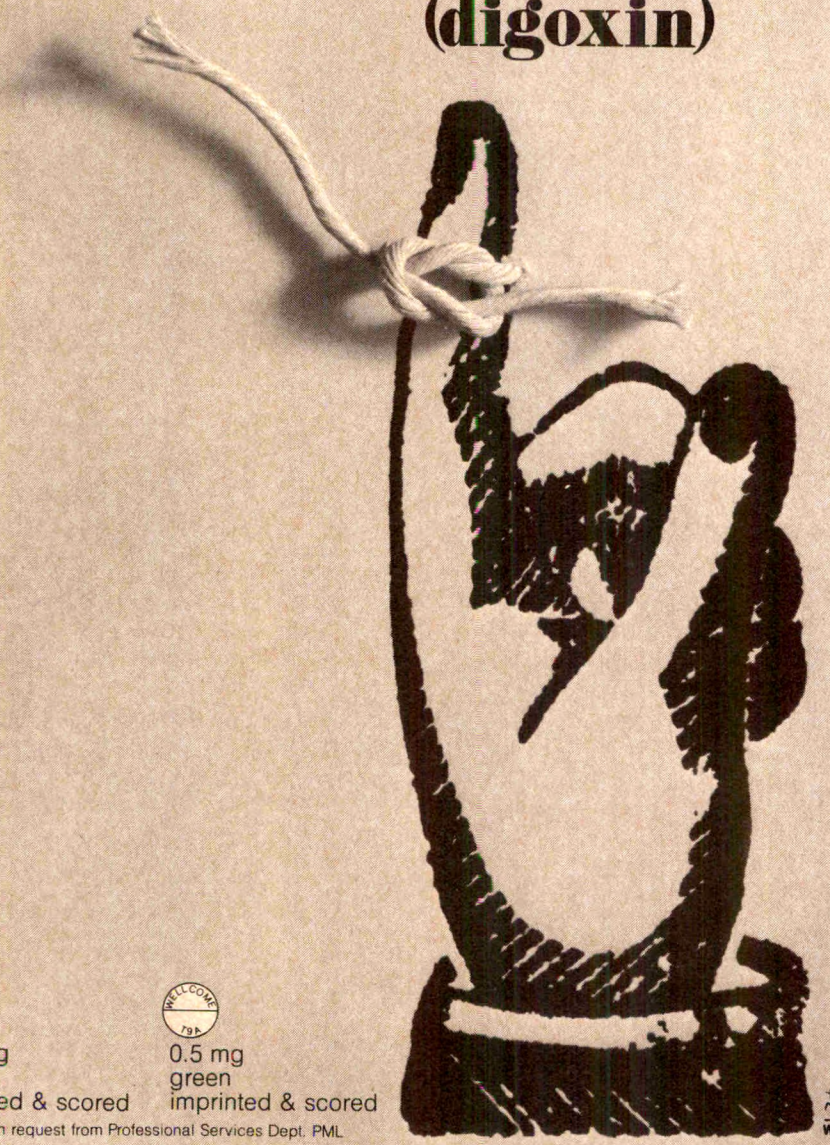
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OCTOBER 197

The American Journal of CARDIOLOGY

VOLUME 3

NUMBER

CLINICAL STUDIES

Serial Measurements of Left Ventricular Ejection Fraction by Radionuclide Angiography Early and Late After Myocardial Infarction

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San Diego, California

The left ventricular ejection fraction was determined serially with radi isotope angiography in 63 patients with acute myocardial infarction. Aft the peripheral injection of a bolus of technetium-99m, precordial radi activity was recorded with a gamma scintillation camera and the ejecti fraction calculated from the high frequency left ventricular time-activi curve. Since this technique requires no assumptions with respect to l ventricular geometry, it is particularly useful in patients with segmen left ventricular dysfunction. Serial measurements during the first 5 da after hospital admission were made in 50 patients, 30 of whom we studied during the subsequent 2 to 39 months (mean 19.9 months). La follow-up serial studies were also performed in an additional 13 patie who had only one measurement of the left ventricular ejection fracti during the early postinfarction period.

Early after infarction, the left ventricular ejection fraction was norm (more than 0.52) in only 15 of the 63 patients, and averaged 0.52 ± 0. (standard deviation) in the 27 patients with an uncomplicated infarct. T ejection fraction was reduced in 24 patients with mild to moderate l ventricular failure (0.40 ± 0.05, $P < 0.0001$) and in the 12 patients w overt pulmonary edema (0.33 ± 0.07, $P < 0.0001$). In 35 patients t ejection fraction correlated with the mean pulmonary arterial wed pressure ($r = 0.72$). In 15 patients with normal left ventricular wall moti by heart motion videotracking, the ejection fraction was significan higher (0.53 ± 0.08) than in the 26 patients with regional left ventricu dysfunction (0.41 ± 0.10, $P < 0.0001$). During the early postinfarcti period, the left ventricular ejection fraction improved in 55 percent patients and remained unchanged or decreased in 45 percent. A furth increase in the ejection fraction was noted in 61 percent of patients dur the late follow-up period. Patients with an initially low or decreas ejection fraction had a significantly greater incidence of early morta and left ventricular dysfunction ($P < 0.02$) than those whose ejecti fraction was normal or improved to normal early after infarction. The data indicate that the ejection fraction is a sensitive indicator of l ventricular function after acute myocardial infarction and that se measurements are helpful in predicting early mortality and morbidity

From the Division of Nuclear Medicine, Department of Radiology and Division of Cardiology, Department of Medicine, University of California Medical Center, San Diego, Calif. 92103. This study was supported in part by Myocardial Infarction Research Unit Contract NOI-HV-81332 and Arteriosclerosis Grant HL 14197 from the National Heart and Lung Institute, Bethesda, Md. Manuscript received January 9, 1976; revised manuscript received April 5, 1976, accepted April 7, 1976.

* Teaching scholar of the American Heart Association.

Address for reprints: Robert A. O'Rourke, MD, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, Texas 78284.

ABLE I

tients With Left Ventricular Ejection Fraction Determined Early and Late After Myocardial Infarction

	Number of Patients (no.)	Age (yr)		Early Postinfarction Period			Late Follow-up Period		
				Studies per Patient		Total Studies	Studies per Patient		Total Studies
		Mean	Range	Mean	Range		Mean	Range	
Group A	20	60	(41–82)	2.9	2-4	58	...	...	...
Group B	30	56	(38–73)	2.6	2-5	79	2.1	(1–6)	62
Group C	13	57	(37–82)	1	...	13	1.3	(1–3)	17
All groups	63	57	(37–82)	2.3	2-5	150	1.8	(1–6)	79*

Groups B and C only.

roup A was studied serially within the first 5 days after infarction; Group B was studied serially early (within the first 5 days) and 2 to 39 nths (mean 19.9 months) after infarction; Group C was studied serially during the late follow-up period 2 to 35 months after the acute in- tion [mean 13.9 months] with only one study during the first 5 days after infarction.

here is clearly a need for noninvasive techniques that ll permit sequential study of left ventricular perfor- ance early after an acute myocardial infarction and ring subsequent convalescence. Accurate sequential ninvasive studies would provide information re- rding changes in left ventricular function and the fects of therapeutic interventions and could yield edictive data concerning morbidity and mortality in tients with a recent myocardial infarction.

The indirect measurement of systolic time intervals m high speed electrocardiographic, phonocardio- aphic and indirect carotid arterial pulse recordings s been proposed as a useful method for detecting anges in left ventricular performance after acute ocardial infarction.[1,2] However, systolic time inter- ls are affected by many factors, exhibit wide indi- lual variations and often are not helpful in assessing t ventricular performance in patients with recent ocardial infarction.[2,3] Recently, single probe unidi- tional echocardiography has been utilized as a non- asive method for determining left ventricular vol- es, ejection fraction and mean rate of internal di- eter shortening (mean Vcf), assuming that the re- ded segmental function is representative of the entire amber.[4] However, abnormal regional wall motion curs in most postinfarction patients and alterations left ventricular chamber size and shape may lead to erroneous estimation of left ventricular volumes en data are derived from a single standardized nocardiographic beam recording.[5] A different non- umatic approach to the measurement of ejection ction has recently been used by Van Dyke et al.[6] eir technique is virtually free of assumptions with spect to left ventricular geometry, and the ejection ction is derived from instantaneous changes in pre- dial count rates as an intravenously administered dioactive tracer travels through the left ventricle. The ction fraction obtained by this method correlates well th the ejection fraction measured by single plane ntriculography[7,8] and, in a recent study in our labo- ory, with the ejection fraction calculated from bi- ne cineventriculograms.[9]

Ease of performance, use of a physiologically inert dioactive tracer with a short effective half-life and edom from geometric assumptions make this tech- nique particularly useful in patients with acute myo- cardial infarction. For these reasons, we employed this virtually noninvasive method to assess left ventricular performance serially during the first few days after myocardial infarction and during subsequent follow- up.

Material and Methods

Sixty-three consecutive patients with acute myocardial infarction admitted to the University of California, San Diego Myocardial Infarction Research Unit were studied. Their ages ranged from 37 to 78 years (mean 57.4 years); 50 patients (79 percent) were male. Acute myocardial infarction was diag- nosed when at least two of the following criteria were present: (1) a history of typical prolonged chest pain; (2) evolution of electrocardiographic changes of acute transmural infarction; and (3) characteristic serial elevations of serum enzymes (creatine phosphokinase [CPK], glutamic oxaloacetic trans- aminase [GOT] and lactic dehydrogenase [LDH]). Thirteen of these patients (21 percent) had a previous myocardial in- farction. Informed and written consent was obtained before each study.

In this study the early postinfarction period was defined as the first 5 days after the onset of chest pain; the late follow-up period ranged from 2 to 39 months. In 50 patients ejection fraction was measured in the coronary care unit on at least two occasions during the early postinfarction period, and in 30 of these patients measurements were repeated during the late follow-up period. Late follow-up data were also obtained in an additional 13 patients who were studied only once during the first 5 days after acute myocardial infarction (Table I).

Radionuclide angiocardiography and determination of left ventricular ejection fraction were performed as described previously.[9] In brief, technetium-99m (10 to 14 mCi of sodium pertechnetate in approximately 1 ml of 0.9 percent sodium chloride) was injected rapidly either into the pulmonary artery through a Swan-Ganz catheter or into a peripheral vein (jugular or large antecubital vein). As the ^{99m}Tc bolus dose traveled through the heart, precordial activity was recorded in a 30° right anterior oblique projection with a gamma scin- tillation camera (Searle Pho-Gamma HP) equipped with a 4,000 parallel hole, high resolution low energy collimator. All image data were initially stored in a digital "list mode" or magnetic tape (Searle Data Storage/Playback Accessory) and subsequently transferred to a small dedicated digital com- puter (MED II, General Electric Corporation). The radio- nuclide angiogram was displayed on the computer oscilloscope in a 64 by 64 matrix and "regions of interest" were assigned with a light pen to the left ventricular blood pool and to the

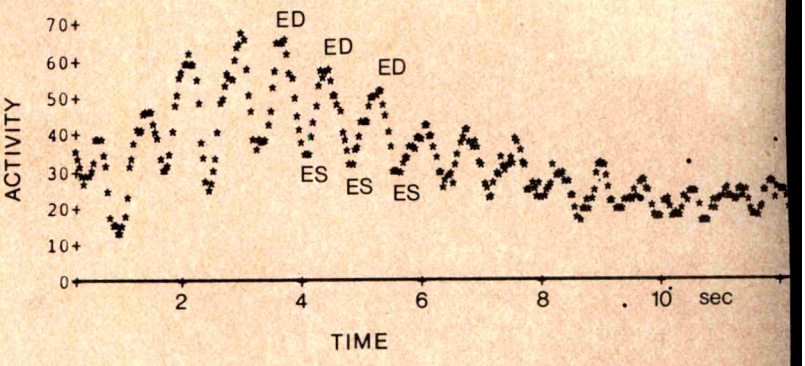


FIGURE 1. Computer printout of a typical left ventricular high frequency time-activity curve corrected for background interference. Each curve point is equal to the number of counts collected in 40 msec. The cyclic fluctuations of the curve correspond to the cyclic changes in the left ventricular volume. Each peak correlates to end-diastole (ED), each valley to end-systole (ES). With use of the early downslope of the curve, the ejection fraction is calculated from the difference in counts between end-diastole and end-systole divided by the counts at end-diastole.

surrounding background area. High frequency data time-activity curves (25 points/sec) were generated from both regions and corrected for camera dead-time losses. After adjustment of the left ventricular time-activity curve for background interference (for example, by subtracting the normalized background time-activity curve from the left ventricular time-activity curve), ejection fraction was calculated from the high and low points on the early downslope of the curve (corresponding to end-diastole and end-systole) (Fig. 1).

In this study, instantaneous counting rates for each curve point were relatively low, ranging from 50 to 150 counts for each 40 msec curve point. Whereas in theory it seems possible to derive ejection fraction only from the curve points at end-diastole and end-systole, the low count rates would be expected to introduce significant statistical errors. In order to put less reliance on single curve points, all curve points throughout at least two and usually three to four cardiac cycles were approximated with a sine wave function and its amplitude was used to determine end-diastolic and end-systolic values. One recognizes that left ventricular volume changes during the cardiac cycle do not, in fact, follow a pure sine wave function, but rather a complex function composed of sine waves, triangular waves and square waves. Nevertheless, the sine wave function appeared to resemble best the cyclic changes in count rates on the left ventricular time-activity curve and permitted accurate calculation of the left ventricular ejection fraction with considerably improved statistical reliability. Thus, as reported previously, ejection fraction obtained with this radionuclide technique closely correlated with ejection fraction determined with biplane cineventriculography.[9] In this study, the value of 0.52 was considered to be the lower limit of the normal ejection fraction.[10]

Determination of the left ventricular ejection fraction with this technique is highly reproducible even if the radioactive bolus dose is administered at different sites. As reported previously,[9] ejection fraction determined in six patients after bolus administration into the superior vena cava correlated closely with the ejection fraction obtained in the same six patients after the radioactive tracer was injected through a peripheral vein 24 hours later (r = 0.96; mean difference 6.4 percent).

During the early postinfarction period, the ejection fraction was compared with the mean pulmonary arterial wedge pressure as an index of left ventricular filling pressure in 35 patients and with the cardiac index and stroke volume index in 28 patients. The mean pulmonary arterial wedge pressure was measured immediately before the isotope study through a flow-directed balloon-tipped catheter positioned appropriately under fluoroscopic monitoring.[11] Cardiac output and stroke volume were determined by the thermodilution method[12] within 2 hours of measurement of the ejection fraction. Roentgenographic assessment of the external le heart dimension as an index of left ventricular size and hea motion videotracking for the analysis of left ventricular wa motion were performed during the early postinfarction perio and during the early and late follow-up periods with metho described previously.[13,14] The left heart dimension was de termined by measuring the distance from the midline to th widest point on the left heart border on a standardized ele trocardiogram-triggered, end-diastolic chest X-ray film durin an inspiration of 1,000 ml above the patient's functional re sidual capacity.[13]

Left ventricular wall motion was assessed with a 23 cr image intensifier, a Plumbicon television camera and the hea motion videotracker (Biotronix).[14] After a standard inspira tion, motion of the border of the left ventricle was recorde from high, mid and low sites in the frontal, lateral and 15° le and right anterior oblique projections. The movement of th selected sites was analyzed with respect to amplitude an velocity and classified according to a modification of the te minology employed previously by Herman and Gorlin.[1] Dyskinesia was defined as paradoxical systolic outward mo tion, hypokinesia as a 50 percent or greater reduction of wa motion compared with normal segments, and akinesia as ab sence of wall motion.

During late follow-up a patient was considered to have le ventricular dysfunction when two of the following signs wer

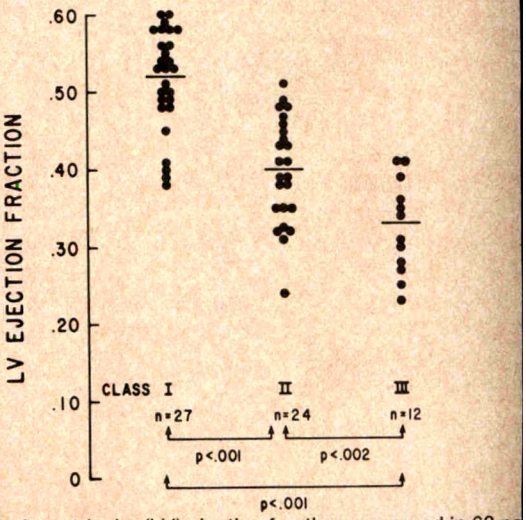


FIGURE 2. Left ventricular (LV) ejection fraction, measured in 63 pa tients early after acute myocardial infarction, compared with the pa tients' clinical class (see text). The **horizontal line** in each colum represents the average value. The statistical differences among classe I, II and III are expressed by the *P* values (nonpaired *t* test).

TABLE II

Clinical Class and Hemodynamic Measurements in 34 Patients Early After Acute Myocardial Infarction

	Class I		Class II		Class III	
Patients (no.)	13	P*	10	P†	11	P‡
Mean pulmonary arterial wedge pressure (mm Hg)	11.9 ± 1.1	NS	14.4 ± 1.4	NS	17.8 ± 2.0	<0.02
Cardiac index (liters per min/m²)	2.8 ± 0.2	NS	2.7 ± 0.2	<0.02	2.0 ± 0.2	<0.01
Stroke volume index (ml/beat per m²)	37.2 ± 3.0	NS	30.4 ± 2.1	<0.008	21.2 ± 2.2	<0.005
Ejection fraction	0.49 ± 0.02	<0.05	0.43 ± 0.02	<0.002	0.33 ± 0.02	<0.0001

Each value represents the average and 1 standard error of the mean.
* Level of significance for the difference between classes I and II; † level of significance for the difference between classes II and III; ‡ level of significance for the difference between classes I and III.
NS = not significant; *P* = probability.

resent: (1) cardiomegaly, (2) bibasilar rales, and (3) a third eart sound.

For statistical analysis of the data Student's *t* test for aired and unpaired data and standard regression equations ere used.

Results

arly Postinfarction Studies

Ejection fraction compared with early clinical nd hemodynamic findings: In the 63 patients, ejection fraction obtained during the early postinfarction eriod (the first 5 days) averaged 0.44 ± 0.10 (standard eviation). The ejection fraction was normal in only 15 atients and reduced (less than 0.52) in the remaining 8 patients (76 percent). This reduction in ejection raction was clearly reflected in the patients' status sing the clinical classification employed by the National Heart and Lung Institute Myocardial Infarction Research Units[16] (Fig. 2). Thus, in 27 patients in class without evidence of congestive heart failure, the jection fraction averaged 0.52 ± 0.05 and was normal n 15 (56 percent) of these patients. Significantly lower jection fractions were observed in the 24 patients in lass II with signs of mild to moderate left ventricular ailure (average of 0.40 ± 0.05, $P < 0.001$); none of these atients had a normal ejection fraction. In the 12 patients in class III with overt pulmonary edema the jection fraction was more severely depressed, averaging nly 0.33 ± 0.07 ($P < 0.0001$); none of these 12 patients ad a normal ejection fraction.

The ejection fraction was inversely related to the ean pulmonary arterial wedge pressure, measured in 5 patients ($r = -0.72$). Furthermore, in 28 patients who ad cardiac output measurements during the early ostinfarction period, the cardiac index ranged from 1.4 o 4.3 liters/min per m² body surface area (mean 2.5) nd the stroke volume index from 11 to 60 ml/beat per n² (mean 31.2). However, both of these hemodynamic easures correlated poorly with the ejection fraction r values of 0.47 and 0.54, respectively), and the ejection raction was often reduced in the presence of a normal ardiac index and stroke volume index. This correlation id not improve when the stroke work index was substituted for the cardiac index or stroke volume index ($r = 0.48$).

Among the hemodynamic measures, the ejection fraction separated the three clinical classes best. Thus, in 34 patients whose cardiac output was measured, only the ejection fraction was significantly different among all three classes (Table II). The interclass differences for the mean pulmonary arterial wedge pressure were not significant.

Serial changes in left ventricular ejection fraction during the early postinfarction period: Among the 50 patients with early serial measurements, ejection fraction improved during the early postinfarction period in 27 (54 percent), deteriorated in 13 (26 percent) and remained unchanged in 10 (20 percent). These changes occurred within an average time of 1.9 days. By the end of the early postinfarction period, the ejection fraction had returned to normal in eight patients but had decreased from normal to reduced in four.

For the entire patient group these individual changes resulted in a moderate, but not significant, increase in the ejection fraction during the early postinfarction period (Table IIIA), whereas the heart rate was unchanged, the mean arterial pressure reduced by an average of 10.5 percent ($P < 0.001$) and the external left heart dimension slightly but significantly decreased ($P < 0.01$). These changes in ejection fraction were analyzed further in 12 patients whose ejection fraction improved and who also had other hemodynamic studies (Fig. 3). In these 12 patients, this improvement ($P < 0.002$) was

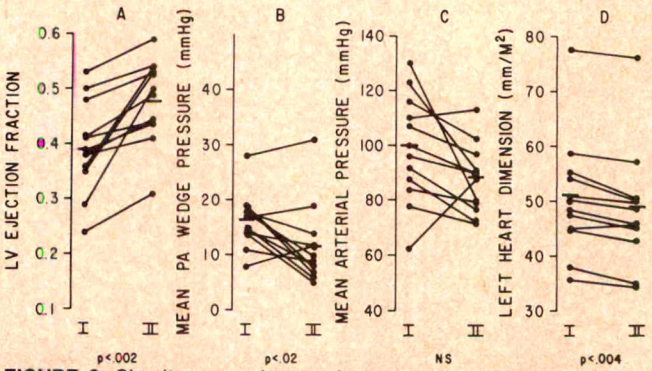


FIGURE 3. Simultaneous changes in mean pulmonary arterial (PA) wedge pressure, mean arterial blood pressure and external left heart dimension in 12 patients whose left ventricular (LV) ejection fraction improved during the early postinfarction period (see text).

associated with decreases in mean pulmonary arterial wedge pressure ($P < 0.02$) and external left heart dimension ($P < 0.004$) but no significant changes in average heart rate or mean arterial pressure. Nevertheless, individual variations occurred; for example, mean pulmonary arterial wedge pressure increased in three patients and the external left heart dimension in one patient.

Table IIIA relates the changes in left ventricular ejection fraction to drug therapy during the early postinfarction period. Values for ejection fraction showed a moderate but significant improvement over values in untreated patients only in the 31 patients who received digitalis, diuretic drugs or antihypertensive drugs, alone or in combination.

Changes in mean pulmonary arterial wedge pressure during the early postinfarction period did not consistently reflect changes in ejection fraction. For example, in 10 patients with initial mean pulmonary arterial wedge pressures that were abnormally elevated (12 to 20 mm Hg), a subsequent decrease was associated in each instance with an increase in the ejection fraction. However, in two patients, mean pulmonary arterial wedge pressures were reduced from 24 and 35 mm Hg to 3 and 27 mm Hg, respectively, whereas the ejection fraction remained unchanged. In four patients with initially normal or decreasing pulmonary arterial wedge pressures, the ejection fraction decreased in two, but increased in the other two patients. There was an inconsistent relation between changes in the external left heart dimension and the ejection fraction. In seven patients, a decrease of the left heart dimension from an initially enlarged value (more than 52 mm/m^2 body surface area) was associated with an improvement of the ejection fraction. However, in nine patients with an initially normal left heart size, a further decrease was accompanied by an increase in ejection fraction in only six patients.

Relation of ejection fraction to abnormal wall motion: Left ventricular wall motion was analyzed in the early postinfarction period in 41 patients. No anterior or lateral wall motion abnormalities were detected in 15 patients (36 percent) and the average ejection fraction in these patients was higher (0.53 ± 0.08) than in the remaining 26 patients who exhibited segmental left ventricular hypokinesia, akinesia or dyskinesia (average 0.41 ± 0.10, $P < 0.0001$).

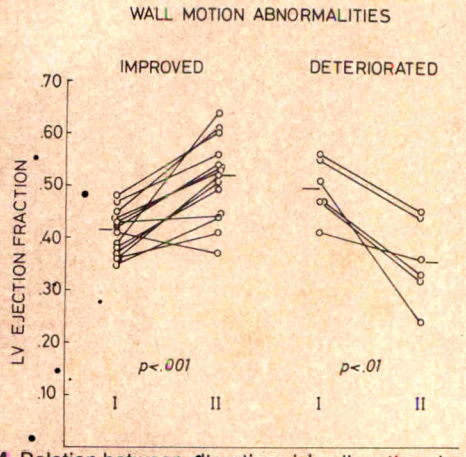
Late Follow-up Studies

Ejection fraction related to heart rate, blood pressure and drug therapy: In the 43 patients with measurements during the late follow-up period (2 to 39 months, mean 19.7 months) after acute myocardial infarction, ejection fraction had increased from 0.45 ± 0.02 at the end of the early postinfarction period to 0.49 ± 0.01 ($P < 0.01$). This increase was accompanied by a significant reduction in heart rate and a significant increase in mean arterial blood pressure (Table IIIB). During this time period, the ejection fraction increased in 26 patients (61 percent), decreased in 10 (23 percent), and remained unchanged in 7 patients (16 percent).

TABLE III
Changes in Ejection Fraction During the Early Postinfarction and Late Follow-up Periods (average ± 1 standard error of the mean)

	Patients (no.)	Ejection Fraction			Heart Rate (beats/min)			Mean Arterial Pressure (mm Hg)			External Left Heart Dimension (mm/m^2)		
		I	II	P*	I	II	P*	I	II	P*	I	II	P*
A. Early Postinfarction Period													
All Patients	50	0.42 ± 0.03	0.45 ± 0.01	NS	85 ± 3	88 ± 2	NS	100 ± 2	88 ± 2	<0.0001	50.7 ± 1.2	49.4 ± 1.2	<0.01
No Treatment	19	0.46 ± 0.02	0.46 ± 0.02	NS	75 ± 2	79 ± 2	NS	94 ± 2	86 ± 2	<0.008	49.3 ± 1.6	47.5 ± 1.6	NS
Treatment†	31	0.39 ± 0.02	0.43 ± 0.02	<0.01	89 ± 3	93 ± 3	NS	100 ± 3	88 ± 3	<0.002	51.6 ± 1.7	50.6 ± 1.7	NS
B. Late Followup Period													
All Patients	43	0.45 ± 0.02	0.49 ± 0.01	<0.01	82 ± 2	75 ± 2	<0.002	91 ± 3	103 ± 2	<0.003	48.9 ± 1.0	47.3 ± 1.3	NS
No Treatment	14	0.46 ± 0.02	0.53 ± 0.02	<0.02	81 ± 4	74 ± 3	<0.04	88 ± 3	105 ± 6	<0.03	47.0 ± 1.4	45.1 ± 1.5	<0.02
Treatment†	29	0.43 ± 0.02	0.47 ± 0.02	NS	82 ± 3	75 ± 2	<0.02	93 ± 3	102 ± 2	<0.02	49.9 ± 1.2	48.5 ± 1.6	NS

* Level of significance for the change between the initial and follow-up studies.
† Digitalis, diuretic agents or antihypertensive drugs alone or in combination.
I = initial, II = follow-up study during each study period; NS = not significant; P = probability.



GURE 4. Relation between alterations in wall motion abnormalities nd left ventricular (LV) ejection fraction when measured during the first days (I) and 2 to 39 months (average 19.4 months) (II) after myocardial farction. The **horizontal line** in each column represents the mean lue. Data at left and right are, respectively, from patients whose gmental wall motion improved and deteriorated (see text).

jection fraction did not improve significantly in the atients who required treatment, whereas a significant nprovement occurred in the 14 nontreated patients Table IIIB).

Ejection fraction related to wall motion abnormalities: Subsequent follow-up studies showed a rather onsistent relation between alterations in left ventricular wall motion and changes in ejection fraction. Improvement or deterioration of segmental wall motion bnormalities during the late follow-up period was defined as follows: (1) disappearance or appearance of bnormal wall motion; (2) a decrease or increase in the umber of recorded sites exhibiting abnormal wall notion; and (3) a change from dyskinesia to hypokinesia r akinesia, from hypokinesia to akinesia or vice-versa. Among the patients with sequential wall motion studies uring the early postinfarction and follow-up periods all motion was not altered in 16 patients (48 percent), ad deteriorated in 6 (17 percent) and improved in 13 37 percent). Ejection fraction did not change significantly when no alterations in wall motion occurred, but ecreased significantly ($P < 0.01$) when wall motion bnormalities deteriorated or occurred for the first time uring the follow-up period (Fig. 4). Conversely, ejection raction significantly increased ($P < 0.001$) when wall notion abnormalities either improved or disappeared.

jection Fraction and Morbidity and Mortality During arly and Late Postinfarction Periods

To relate the early changes in ejection fraction to the ubsequent clinical course, patients were classified into wo groups: group I, 18 patients whose ejection fraction as either normal or improved to normal during the arly postinfarction period, and group II, 32 patients hose ejection fraction was either reduced or decreased om normal during this period (Table IV). All patients ho died within less than 60 days after acute myocardial

TABLE IV

Early and Late Mortality of Patients with Serial Ejection Fraction (EF) Measurements During the Early Postinfarction Period

	Group I: Early EF Normal or Improving to Normal	Group II: Early EF Low or Decreasing to Low
Patients (no.)	18	32
Early mortality (<60 days)	0	6
Causes of death		
Congestive heart failure	...	3
Sudden death	...	2
Myocardial rupture	...	1
Late mortality (>60 days)	3	7
Causes of death		
Recurrent myocardial infarction	...	4
Sudden death	2	2
Bronchopneumonia	1	1

infarction were in group II; there were no early deaths among the 18 patients in group I. Moreover, 6 months after the acute myocardial infarction, 64 percent of patients in group II had clinical signs of left ventricular dysfunction compared with only 31 percent of patients in group I ($P < 0.02$). This difference between the two groups became less pronounced during further follow-up, and 24 months after infarction the incidence rate of left ventricular dysfunction was similar for both groups (29 percent in group I and 31 percent in group II). However, only 34 patients have been followed up for 12 months and only 20 patients for 2 years or more. Ten patients died during the late follow-up period, three in group I and seven in group II. The remaining patients have been followed up for less than 24 months after infarction. Similarly, there was no significant difference in the average ejection fraction between the two groups when studied an average of 19.7 months after the acute myocardial infarction (0.51 ± 0.03 in group I versus 0.48 ± 0.02 in group II).

Discussion

Advantages of radionuclide measurement of ejection fraction: In this study, serial measurements of left ventricular ejection fraction were used to assess changes in left ventricular performance early and late after acute myocardial infarction. Ejection fraction was determined by a "nontraumatic" radionuclide technique. On the basis of previous comparisons with single[7,8] and biplane cineventriculographic measurements,[9] this radionuclide technique permits accurate and reproducible determinations of the ejection fraction in patients with valvular heart disease or coronary artery disease with and without regional left ventricular dysfunction. Unlike electrocardiographically gated scintigraphy,[17,18] which utilizes the area-length method for analysis, the currently employed technique requires no assumptions regarding chamber geometry, an important consideration in view of the high rate of wall motion abnormalities in patients with acute myocardial in-

farction. The use of different injection sites for the radioactive tracer during the serial studies—the antecubital or jugular vein or, when available, through a flow guided catheter into the pulmonary artery—has little if any effect on the results, as shown previously by Steele et al.[8] and in our laboratory.[9]

Because the ejection fraction is calculated from the initial passage of the tracer through the heart, all recordings are made within less than 60 seconds; thus, one can use readily available radioactive tracers such as ^{99m}Tc-pertechnetate or—if subsequent infarct imaging is desired—^{99m}Tc-pyrophosphate.[19] The short intravascular half-life of these agents, moreover, permits repeat studies at relatively short time intervals. Conversely, selecting ^{99m}Tc-human serum albumin as the tracer with a longer intravascular half-life permits additional left ventricular wall motion analysis by electrocardiographically-gated scintigraphy.[17]

Left ventricular ejection fraction during the early postinfarction period: relation to hemodynamic measurements and abnormal wall motion: Left ventricular performance after an acute myocardial infarction has been described previously in terms of left ventricular filling pressure, cardiac output, stroke volume and stroke work.[20–23] In general, these hemodynamic indices were consistent with the clinical findings, although discrepancies occurred in individual patients. Thus, in a study by Hamosh and Cohn,[24] patients with uncomplicated infarction frequently exhibited abnormal elevations of the left ventricular filling pressure and, in patients in shock, these increases ranged from mild to severe. Similarly, normal values for cardiac output, stroke volume and stroke work have been reported in patients with heart failure or even shock.[20,24,25]

Among the factors that alter left ventricular performance after acute myocardial infarction, two are likely to be of major importance: (1) the extent and compliance of the infarcted and noncontractile region; and (2) the functional state of the residual noninfarcted myocardium.[26–33] Therefore, measurement of left ventricular filling pressure alone or of cardiac output, stroke volume or stroke work may not reliably reflect the true functional state of the left ventricle. For instance, to deliver a normal stroke volume, the stiff left ventricle appears to operate from a higher end-diastolic pressure, whereas the more compliant chamber is likely to increase its end-diastolic volume.[33]

These compensatory mechanisms may serve to explain the lack of a better agreement in our study between commonly used hemodynamic measures such as mean pulmonary arterial wedge pressure, cardiac output and stroke volume index and the ejection fraction. Although the mean pulmonary arterial wedge pressure does not always accurately reflect the true left ventricular end-diastolic pressure,[34] this limitation is unlikely to account entirely for its relatively poor correlation with the ejection fraction. Cardiac index, stroke volume index and stroke work index agreed even less well with the left ventricular ejection fraction. Although these measurements were not obtained simultaneously with the ejection fraction and therefore could have changed during the time between the hemodynamic and radi nuclide determinations, such changes in a large numb of patients would tend to be random and would n explain the lack of a better agreement. On the oth hand, the same stroke volume can be delivered from small or a large left ventricular chamber. The ejectio fraction, however, represents the ratio of stroke volum to end-diastolic volume and therefore is not necessari proportional to the stroke volume.

Moreover, by relating the stroke volume to the en diastolic volume, the left ventricular ejection fractio appears to be a more sensitive index of left ventricul performance in postinfarction patients. In this stud it permitted better separation of the patients' clinic classes than did the other hemodynamic measures. Th slight degree of overlap between the ejection fractio in the different clinical classes (Fig. 2) can be attribute to the subjective nature of the clinical classification. A indicated earlier, a reduced ejection fraction may occu in patients with a normal cardiac index and mean pu monary arterial wedge pressure.

Among the 63 patients studied early after the acu myocardial infarction, the ejection fraction was reduce in 47 patients (75 percent). Even in the 27 patien without physical findings suggestive of left ventricul dysfunction, the ejection fraction was normal in only 1 it was not normal in any patient with signs of mild t moderate left ventricular failure and averaged only 0.3 in patients with overt pulmonary edema. These findin are consistent with a recent study by Rigo et al.,[18] an suggest that the ejection fraction is a sensitive indicat of impaired left ventricular function after an acu myocardial infarction.

The extent of depression of left ventricular perfo mance appears to be quantitatively related to the exte of abnormal regional wall motion as assessed by cin ventriculography[35] and by gated scintiphotography. The noninvasive analysis of wall motion by vide tracking employed in our study does not permit quantitative description of the extent of abnorm segmental wall motion and often does not detect the le common wall motion disorders involving septal or di phragmatic portions of the left ventricular surfac Nevertheless, the patients with normal wall motion b videotracking had significantly higher ejection fractio than those with wall motion abnormalities.

Serial changes in left ventricular ejection fra tion during the late follow-up period: Althou previous reports[23,35–41] concerning changes in le ventricular function during the early convalescent pha after an acute myocardial infarction have been som what conflicting, most suggest that improvement occu in the majority of patients. Thus, in recent studies b Rahimtoola et al.,[40] left ventricular end-diasto pressure decreased and left ventricular stroke wo increased in 55 percent of patients between the 2nd da and 3 to 8 weeks after the acute myocardial infarctio During a similar interval, Rigo et al.[18] observed an i crease in ejection fraction in 14 of 20 patients. In o study, the ejection fraction improved in 54 percen deteriorated in 26 percent and remained unchanged

0 percent of patients within the first 5 days after the cute infarction. In 43 patients subsequent measurements after the acute myocardial infarction showed an nchanged left ventricular ejection fraction in 16 percent, deterioration in 23 percent and further improvement in 61 percent compared with measurements obained during the last study during the early postinarction period. Nevertheless, the ejection fraction for he entire patient group showed significant, although nly moderate improvement (by 8.9 percent) ($P < 0.01$) etween the end of the early postinfarction period and he late follow-up study, whereas mean arterial blood ressures increased significantly. These data do not ermit identification of a specific cause for the late hange in ejection fraction. However, experimental tudies suggest that scar formation may play an imortant role.[30] Reduction in heart size and wall motion bnormalities may also contribute to this finding.

In contrast to the serial changes in ejection fraction uring the late follow-up period, when a significant nprovement was observed only in the patients who equired no drug therapy (Table III), ejection fraction uring the early postinfarction period improved sigificantly only in the patients who were treated with iuretic agents, digitalis or antihypertensive drugs eiher alone or in combination (Table III). Therefore, it ppears that the improvement in left ventricular perrmance early after the acute myocardial infarction was he result of drug-related alterations in ventricular oading conditions or enhanced contractile state of the emaining intact myocardium.

Thus, as indicated earlier, the ejection fraction tended improve during serial outpatient studies in patients hose wall motion abnormalities decreased or whose left eart dimension either decreased or became normal. In ntrast, the ejection fraction tended to remain abrmal in patients who manifested new wall motion bnormalities or persistent cardiomegaly during late llow-up studies. These data indicate that left ventricular performance in patients with persistent cardiomegaly and wall motion abnormalities is unlikely to improve during long-term follow-up.

Serial changes in ejection fraction related to subsequent morbidity and mortality: Of the 63 patients included in this study, 16 died during the follow-up period. Serial changes in ejection fraction were closely related to mortality during the early convalescent period (the first 60 days after the acute myocardial infarction). During this time, no patient with a normal or improved ejection fraction died, whereas six of the patients with reduced or a decreased ejection fraction died. In all the patients who died, measurements were made at least 2 days before death and the reduced ejection fraction, therefore, did not reflect the terminal event. However, the level of ejection fraction measured in the first 5 days after infarction was not predictive of late overall mortality, although deaths due to recurrent myocardial infarction were more frequent in the patients with a low ejection fraction during the early postinfarction period. Moreover, at 6 months after the infarct, left ventricular dysfunction was more common in these patients than in those with an initially normal or increasing ejection fraction.

These findings are consistent with previous studies[18,38–41] and suggest that the early serial measurements of ejection fraction are helpful in predicting early morbidity and mortality. Furthermore, serial measurements of the left ventricular ejection fraction during the immediate postinfarction period appeared to be a better measure of the functional state of the left ventricle than serial measurements of the pulmonary arterial wedge pressure or the stroke volume. Since measurement of the ejection fraction by means of the radionuclide method is simple, safe and reliable, further studies employing this technique regarding the effects of therapeutic interventions on left ventricular performance and its relation to early and late morbidity and mortality seem warranted.

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Regional Myocardial Blood Flow During Hyperemia Induced by Contrast Agent in Patients With Coronary Artery Disease

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Regional myocardial specific blood flow (regional specific flow) was measured at rest and during contrast hyperemia after the intracoronary injection of xenon-133. The changes in regional specific flow were transient, resulting in some compromise in one of the underlying restraints of the inert gas washout method, namely, the presence of a steady state. Therefore, to determine the clinical utility of this technique, regional specific flow values obtained with this method were correlated with the presence and severity of coronary artery disease as assessed from the coronary arteriogram and left ventriculogram. Regional specific flow during contrast hyperemia was 186 ± 11 (mean ± 1 standard error of the mean) ml/min per 100 g in control patients and 115 ± 5 in patients with coronary artery disease. There was an inverse relation between regional specific flow during contrast hyperemia and the percent coronary stenosis when the stenosis was 40 percent or greater ($r = 0.70$, $P < 0.001$). Regional specific flow was significantly less in patients with asynergy (77 ± 10 ml/min per 100 g) than in patients with normal ventricular function (105 ± 5) distal to coronary stenoses of greater than 75 percent. Thus, regional specific flow measured during contrast hyperemia using the xenon washout technique and the Anger camera differentiated patients with normal coronary arteriograms from those with coronary artery disease. With this technique, good correlation was shown between regional specific flow and the percent coronary stenosis and presence of ventricular wall abnormalities. The information obtained with this method may provide prognostic information concerning suitability for surgical intervention.

Although coronary arteriography is indispensable for gauging the extent of arterial narrowing and the development of collateral circulation, additional techniques are needed to determine the hemodynamic significance of a given lesion and to gauge residual coronary arterial reserve under the stress of increased myocardial oxygen demand.[1]

Attempts to improve the diagnostic precision of coronary arteriography with parallel measurements of global myocardial specific blood flow using a diffusible indicator and a single probe detector have not met with great success. (The inert gas washout technique provides a measure of blood flow per volume of distribution of the tracer and can be expressed as flow per weight of the tissue receiving the tracer. Therefore, all references to blood flow measurements obtained with this technique are expressed as specific flow, that is, flow/weight of myocardium.) The use of the scintillation camera has circumvented many of these difficulties and supplemented the angiogram by measuring regional myocardial specific blood flow (regional specific flow).[2–4] However, regional specific flow measured at rest is of limited value in the assessment of coronary artery disease, particularly when lesions involve less than 75 percent of the coronary arterial lumen.[5]

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Myocardial blood flow increases after coronary arterial administration of contrast agents.[6–8] After acute coronary stenosis in the dog, the increase in flow is inversely proportional to the degree of stenosis after a critical degree of stenosis has been reached.[6] After the intracoronary injection of radio-labeled macroaggregates, increased heterogeneity in myocardial perfusion can be demonstrated in patients with coronary artery disease.[9]

We have investigated the clinical utility of a directional index of regional myocardial blood flow obtained with xenon-133 during hyperemia induced by administration of contrast agent. Contrast agent-induced vasodilation is a rapidly changing transient event, and thus some error is probably introduced into the blood flow measurements, which require the presence of a steady state. Our aim in this study was to determine whether the index of regional specific blood flow obtained with this method correlated with estimates of the severity of coronary artery disease obtained with coronary angiography and left ventriculography.

Methods

Patient selection: Thirty patients with a stable but usually severe chest pain syndrome undergoing routine diagnostic coronary arteriography were selected at random except that patients with clinical or angiographic evidence of either valve disease or primary myocardial disease were excluded from the study. Informed consent was obtained in all patients before angiography. The patients were evaluated with biplane left ventriculography and selective coronary angiography followed by selective injection of ^{133}Xe into the left coronary artery at rest and again during contrast agent-induced hyperemia. Five of these patients had normal coronary arteriograms and left ventriculograms.

Cardiac catheterization: Each patient was in the fasting state and was premedicated with diphenhydramine, 50 mg, and diazepam, 10 mg, orally or intramuscularly. Right and left heart catheterization with biplane left ventriculography was performed. Selective coronary angiography in multiple projections was then performed using the femoral route. The percent stenosis of the diameter of the coronary arterial lumen was estimated visually by two interpreters utilizing multiple views of the coronary arteries. Only stenoses involving the left anterior descending and left circumflex arteries and their major branches were considered in the data analysis.

Data on left ventricular function were determined from the left ventriculogram. Axis shortening from end-diastole to end-systole was determined from hand-drawn ventriculographic silhouettes. End-diastole was defined as the largest silhouette, end-systole the smallest. Only the first four regularly conducted beats after complete opacification of the ventricle were used. The reproducibility of these silhouettes from one early beat to the next in the same ventriculogram has previously been demonstrated in our laboratory.[10] The lower limits of normal values for axis shortening in our laboratory are greater than or equal to 10 percent shortening in the longitudinal axis in the right anterior oblique projection and to 20 percent shortening in the major transverse axes in both the right anterior oblique and left anterior oblique projections. Posterolateral asynergy was evaluated in the left anterior oblique projection and anteroapical asynergy in the right anterior oblique projection.[11] No attempt was made to evaluate septal asynergy in the left anterior oblique projection because of variable effects on septal motion depending on the level of obstruction in the left anterior descending artery and because flow in the right coronary artery, which usually supplies the posterior septum, was not studied.

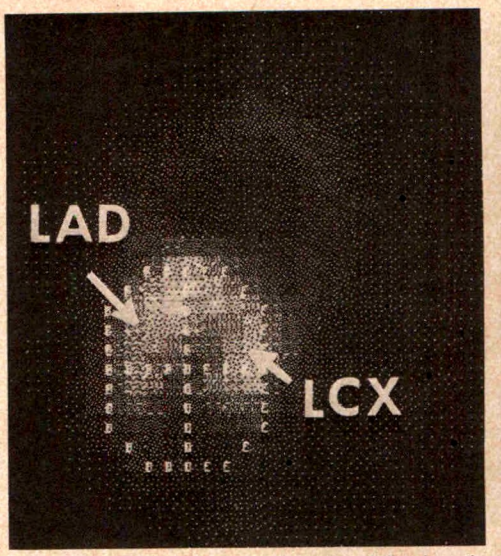


FIGURE 1. Regions of interest over proximal and distal portions of left anterior descending (LAD) and left circumflex (LCX) coronary arteries. The position of these vessels was determined from the initial frame of the gamma camera image while most of the xenon was intravascular.

Measurement of regional myocardial specific blood flow: At least 10 minutes was allowed to elapse between the last injection of contrast agent for diagnostic coronary angiography and the selective injection of xenon. To permit hemodynamic variables to stabilize, at least 30 minutes was allowed to elapse between the last sublingual administration of nitroglycerin and the intracoronary injection of xenon.

The patient was placed in the left anterior oblique position under the fluoroscopic unit, where the center and borders of the heart were marked on the chest. A catheter was placed in the left main coronary artery and its position confirmed by an injection of 0.25 ml of contrast material. The patient was positioned under the scintillation camera in the left anterior oblique position, and 20 to 25 mCi of ^{133}Xe in 2 ml of saline solution was injected; a 3 ml saline flush followed. Washout was monitored with a scintillation camera for 2 minutes after the injection of xenon.

Immediately after the baseline study, a second injection was made into the coronary artery. This injection consisted of 2 cc of Renografin-76® (meglumine and sodium diatrizoate) followed by 20 to 25 mCi of ^{133}Xe, followed by a second bolus dose of 2.5 cc of Renografin-76. Washout was monitored for 1 minute after the injection. The catheter was then removed from the coronary artery; thus, the catheter remained in the left main coronary artery approximately 5 minutes (2 minutes after the first injection, 2 minutes during preparation for the second study and 1 minute after the second injection).

Regional washout curves were obtained by placing electronic cursors over the proximal and distal portions of the left anterior descending and left circumflex coronary arteries (Fig. 1). The position of these vessels was determined from the initial frames of the gamma camera image during the arterial phase of the study, and regional specific flow was calculated from the initial slope of the xenon clearance curve. For the baseline study, washout curves were constructed using 2 second time frames from the peak counting rate to 40 seconds afterward. To minimize possible effects of fat or other non

nuscular components on the calculation of blood flow, only he slope of the curve representing the first 40 seconds of ashout data was computed using a nonweighted, monoexponential least squares program. From the initial slope, nyocardial specific flow in ml/min per 100 g was determined sing the equation

$$F/W = \frac{100\ k\lambda}{\rho}$$

here k was the mean slope calculated from 0 to 40 seconds, was the blood:tissue partition coefficient (assumed to be 72) and ρ was the specific gravity of myocardial tissue (assumed to be 1.05).

Regional specific flow during contrast agent-induced hyeremia was measured from the portion of the washout curve emonstrating augmented flow. Two criteria were used in lecting this portion of the curve: (1) The starting and end oints were defined as those points on the curve where the ope, computed over a 6 second interval, changes most rapdly. (2) The linear regression coefficient (r) for that portion the washout curve extending 6 seconds after the starting oint and 6 seconds immediately before the end point had to e greater than 0.50, thus eliminating elbows from the portion the curve subjected to analysis. The resultant washout curve veraged 15 seconds (range 10 to 20 seconds) and was ubjected to nonweighted least squares analysis to compute he slope. Regional specific flow was then calculated as deribed.

In four patients, reproducibility was determined by perrming two studies using an injection of 2.5 cc of Renografin-76, followed by 25 mCi of ^{133}Xe, followed by 2.5 cc of enografin-76 in each case. Five to 10 minutes was allowed elapse between each study. Specific flow from the four reons of interest was calculated as described.

Regional specific flow values for the distal quadrant verlying the left anterior descending artery and the distal uadrant overlying the left circumflex artery were used for atistical analysis. Regional specific flow during the baseline udy and during contrast agent-induced hyperemia and the hange in regional specific flow within the same quadrant between the two studies were correlated with percent coronary arterial stenosis and left ventricular wall motion. Regression analysis was performed on regional specific flow values and the estimated percent coronary stenosis. For presentation and for analysis of variance, percent stenosis was classified as follows: 25 to 49 percent, 50 to 74 percent, 75 to 99 percent and 100 percent stenosis.

Results

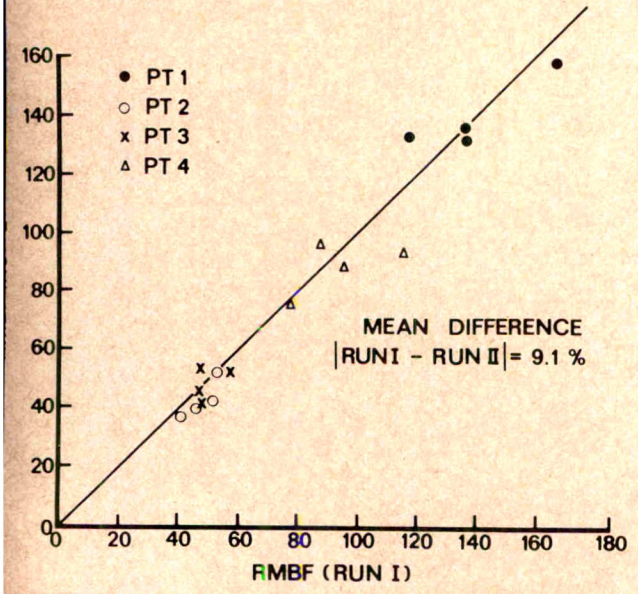
Reproducibility: The mean blood flow obtained in the 16 quadrants (in four patients) was 82.9 ml/min per 100 g during the baseline study (run 1) and 79.6 during the study during contrast hyperemia (run 2) (Fig. 2). The mean percent difference between blood flow obtained during the two studies in the 16 regions of interest was 9.1 percent (Fig. 2).

The reproducibility with which regional specific flow was estimated in a given region during contrast agent hyperemia was represented as the difference between the two pairs of determinations divided by an estimate of the true value of flow, in this case, the average of the pair of determinations. Thus,

$$\text{percent reproducibility} = 2 \cdot \frac{\text{flow 1} - \text{flow 2}}{\text{flow 1} + \text{flow 2}} \times 100$$

Analysis of variance indicated that there was no significant difference between regions in the reproducibility of flow estimation. Thus, the reproducibility of the flow estimate (as the sampling estimate of the standard error) was 9.9 percent.

Baseline regional specific flow: Regional specific flow was 96 ± 10 (mean ± standard error of the mean) ml/min per 100 g in control patients and 65 ± 2 in patients with coronary artery disease. Although these differences were significant ($P < 0.001$), there was considerable overlap between blood flow values in individual patients, and there was no correlation between regional specific flow and the visually estimated percent coronary arterial stenosis (Fig. 3).



GURE 2. Reproducibility of regional myocardial specific blood flow MBF) measurements during contrast hyperemia in four patients. Runs and 2 were both performed during contrast hyperemia with 10 minutes eparating the two studies.

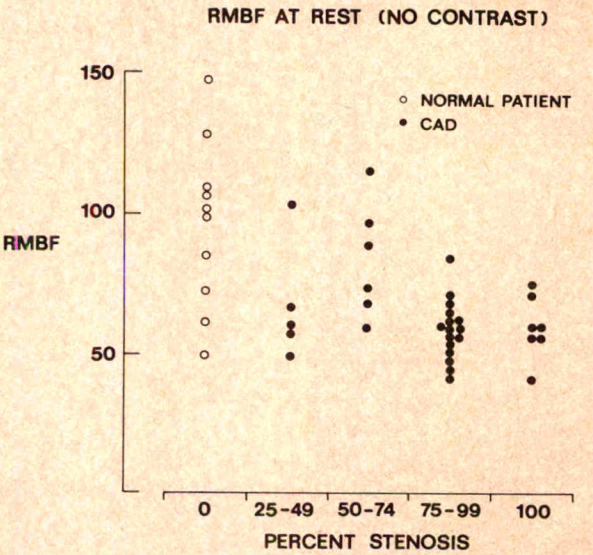


FIGURE 3. Correlation between regional myocardial specific blood flow (RMBF) at rest and percent coronary stenosis. CAD = coronary artery disease.

Regional specific flow during contrast agent hyperemia: Regional specific flow during contrast agent-induced hyperemia was significantly greater in control patients (186 ± 11 ml/min per 100 g) than in patients with coronary artery disease (115 ± 5) (P <0.001). Regional specific flow (in ml/min per 100 g) was 170 ± 14 distal to lesions of less than 50 percent; 129 ± 5 distal to lesions of 50 and 74 percent; 96 ± 6 distal to lesions of 75 to 99 percent; and 95 ± 10 distal to 100 percent stenoses. There was an inverse relation between regional specific flow during contrast agent-induced hyperemia and the percent coronary stenosis when the stenosis was 40 percent or greater (regional specific flow = 197–1.1 [percent stenosis], r = 0.70, P <0.001) (Fig. 4). There were insufficient data points for analysis of less than 40 percent stenosis. The absolute specific flow during contrast agent-induced hyperemia distinguished control patients from patients with coronary artery disease more accurately than regional specific flow at rest. Regional specific flow values distal to stenoses of greater than 50 percent were lower than all but one regional specific flow value in patients with normal coronary arteriograms and lower than all but one flow value distal to stenoses of less than 50 percent. There was no significant difference in regional specific flow distal to stenoses of less than 50 percent and regional specific flow in patients with normal coronary arteriograms.

Increase in regional specific flow during contrast hyperemia: There was an increase of 90 ± 12 ml/min per 100 g in the control patients between the baseline and contrast agent studies. The increase in all patients with coronary artery disease was 50 ± 4 ml/min per 100 g (P <0.01). The increase in regional specific flow (in ml/min per 100 g) was 96 ± 16 distal to lesions of less than 50 percent; 44 ± 12 distal to lesions of 50 to 74 percent; 36 ± 5 distal to lesions of 75 to 99 percent; and 34 ± 9 distal to 100 percent stenoses. Thus, we found an inverse relation between increase in regional specific flow and the percent of coronary stenosis (r = 0.62, P <0.001).

Characteristics of the washout curve during contrast hyperemia: In control patients, there was an initial plateau lasting several seconds immediately after the bolus injection of xenon (Fig. 5). Immediately after the plateau, there was a period of increased xenon clearance lasting 10 to 15 seconds. After this point, the washout rate returned to levels equal to or less than those found during the baseline study.

In patients with coronary artery disease, the initial plateau in the washout curve lasted considerably longer and was followed by a period of increased flow (not as great as that in control patients) and finally by a clearance rate less than or equal to that during the baseline study (Fig. 5).

In the control patients, the initial plateau lasted 1.6 ± 1.0 (standard error of the mean) seconds. In patients with coronary artery disease, the duration of the plateau was 8.0 ± 0.8 second. Thus, the duration of the initial plateau was significantly longer in patients with coronary artery disease (P <0.005). However, the correlation between the duration and the severity of coronary artery disease was weak.

Correlation with ventricular wall function: Wall function was assessed in 13 patients with stenosis of greater than 75 percent involving the left anterior descending or left circumflex coronary artery, or both. In 14 regions involving tissue perfused by the left anterior descending coronary artery, anteroapical asynergy was assessed; in 9 regions involving tissue perfused by the left circumflex artery, posterolateral asynergy was assessed. In 16 regions with coronary stenosis of 75 percent or greater but with normal ventricular function in the tissue perfused by that vessel, regional specific flow was 105 ± 5 ml/min per 100 g. In seven patients with coronary stenosis of greater than 75 percent and with asynergy in that portion of the wall supplied by the stenosed vessel, flow was 77 ± 10 ml/min per 100 g (P <0.01).

Discussion

Myocardial specific blood flow measured at rest with the radioactive xenon washout technique has not been

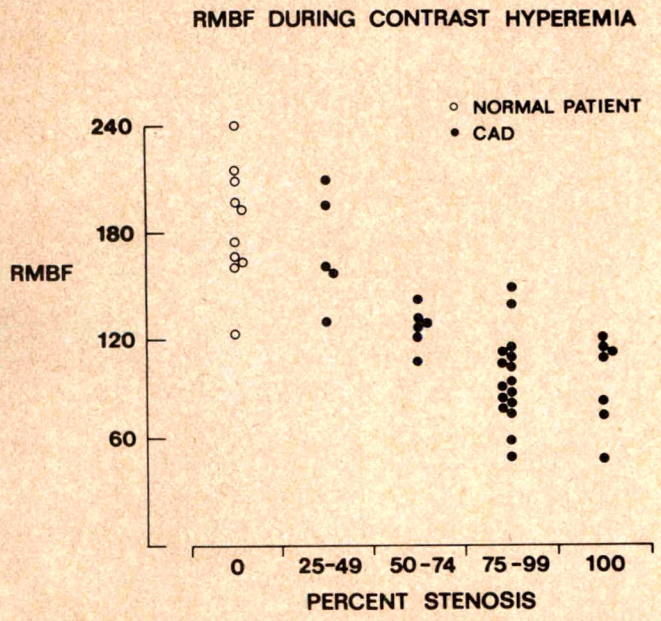


FIGURE 4. Correlation between regional myocardial specific blood flow (RMBF) during contrast hyperemia and percent coronary arterial stenosis. CAD = coronary artery disease.

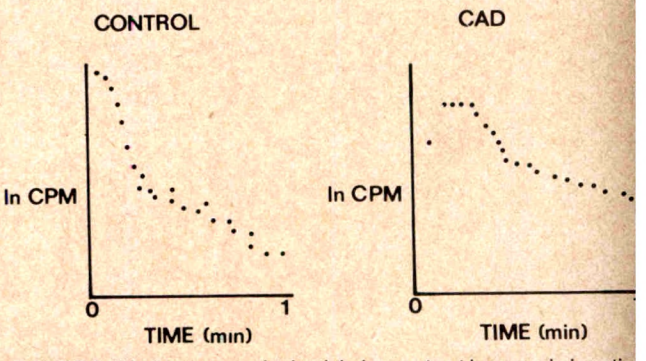


FIGURE 5. Washout curve obtained during contrast hyperemia in patient with normal coronary arteriogram (left) and patient with coronary artery disease (CAD) (right). CPM = counts per minute.

totally adequate indicator for assessing coronary ar-ery disease. When global myocardial specific flow was easured with ^{133}Xe, no significant differences were bserved in whole heart blood flow in patients with or ithout coronary artery disease.[12,13] With the intro-uction of techniques to assess regional myocardial ecific blood flow and coronary sinus sampling tech-iques to assess specific flow, significantly less flow was und in patients with stenosis of greater than 75 per-nt than in patients with normal coronary arterio-rams.[3,5,14] Similarly, in patients with prior transmural farction, decreased myocardial specific flow was found istal to stenoses of greater than 80 percent.[15] Although here is a correlation between regional specific flow btained at rest and the presence of coronary arterial enosis and the presence of asynergy, there is a good eal of overlap between regional specific flow obtained individual patients with normal coronary arterio-rams and in those with coronary artery disease.[5]

As expected, we found considerable overlap between gional specific flow values obtained at rest in patients ith normal coronary arteriograms and in those with oderate or even severe coronary artery disease. herefore, resting studies of regional myocardial blood ow are seriously limited in the additional diagnostic formation they provide in the assessment of coronary rtery disease.

Ritchie et al.[9] have used the intracoronary injection contrast medium to induce vasodilatation and sim-late stress. When myocardial scintigraphy was per-rmed after the coronary injection of contrast agent llowed by radio-labeled macroaggregated albumin, atients with coronary artery disease manifested in-reased heterogeneity in perfusion by comparison with ndings in the baseline study and in normal patients.

We have found that regional specific flow measured uring contrast agent-induced hyperemia may be a nsitive method for detecting hemodynamically sig-ificant coronary arterial lesions in man. Indeed, only ne regional flow value in a patient with a normal cor-nary arteriogram and only one flow value distal to a enosis of less than 50 percent overlapped regional flow alues with hyperemia obtained distal to stenoses of 50 ercent or greater. These observations are in conformity ith results of animal studies[6] demonstrating a reduced apability to increase coronary blood flow during con-ast agent-induced hyperemia when stenoses are more han 40 percent.

Limitations of method: The usefulness and the mitations of the xenon washout technique for mea-uring regional specific flow have been reviewed else-here.[16–20] We point out here only the limitations re-ted to this particular application of the technique. One ssumption of the inert gas washout method is the ex-tence of a steady state during the time of measure-ent. The injection of contrast medium results in a onsteady state with an initial decrease in blood flow particularly in patients with coronary artery disease) llowed by increasing flow and then a return to normal alues. We have attempted to prolong the period of ntrast agent-induced hyperemia by injecting contrast edium both before and after the xenon injection. The washout curves we have obtained appear monoexponential during this increase in washout, lasting approximately 10 to 15 seconds. Nevertheless, there is some deviation from the steady state during this period. In addition, it is possible that the hyperosmotic contrast agent may influence removal of ^{133}Xe from the heart through effects independent of blood flow. This may be the case particularly during the early portion of the washout curve and may be a factor in the initial plateau. In any case, contrast agent may also affect the quantitative accuracy of the blood flow measurement. Thus, applying the inert gas washout method to contrast agent-induced hyperemia represents a qualitative rather than quantitative measure of regional myocardial blood flow.

That the directional changes observed with this technique accurately separated normal patients from those with coronary artery disease and elucidated the factors associated with alterations in myocardial blood flow indicates that the deviation from the steady state during the measurement period is not a major limitation in applying this technique. The degree of overlap between regional specific flow values at rest in patients with normal coronary arteriograms and those with coronary artery disease disappears during contrast agent-induced hyperemia, particularly in patients with stenosis of greater than 50 percent. There is good correlation between regional specific flow and the percent coronary stenosis; similarly, there is significantly less regional specific flow in patients with ventricular asynergy than in patients with normal ventricular function and the same degree of coronary stenosis.

The initial plateau that is observed predominantly in patients with coronary artery disease may represent a reduction in regional specific flow due either to the hyperosmotic effects of contrast agent on the myocardium or to the effect of contrast agent on removal of xenon from the myocardium as previously discussed. The amount of contrast medium that was injected into the coronary artery (5 cc) is less than that injected during routine coronary angiography. However, the evident plateau is not an effect of a bolus injection since the injection of saline solution without contrast medium did not result in an initial period of reduced washout.

Clinical usefulness of method: The value of this technique as an adjunct to the morphologic information provided from coronary angiography depends on its ability to provide information not obtained from contrast procedures. In this regard, some variation in regional specific flow exists in patients who apparently have the same degree of coronary stenosis and similar ventricular wall function. This variability is greater than one would expect from the reproducibility of the technique itself and may indicate that regional specific flow cannot be predicted on the basis of subjective evaluation of the coronary arteriogram. Indeed, it may not be possible to estimate accurately the degree of stenosis by visual assessment of the coronary arteriogram.[21] Therefore, regional specific flow may have prognostic significance in determining the suitability of patients for surgical or medical therapy and in determining the patient's probable outcome.

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Noninvasive Myocardial Imaging With Potassium-43 and Rubidium-81 in Patients With Left Bundle Branch Block

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Noninvasive myocardial imaging with potassium-43 and rubidium-81 has been used successfully to identify areas of infarction and exercise-induced ischemia as regions of decreased radioactivity. The image defects observed are believed to be due to a decreased radionuclide uptake in regions of myocardial scar or to heterogeneous myocardial accumulation of tracer as a result of regional ischemia. Of 27 patients with left bundle branch block studied with noninvasive imaging at rest and during exercise, 25 manifested at rest reduced radioactivity in the region of the interventricular septum. This pattern is similar to that seen in patients with anteroseptal myocardial infarction. Sixteen of the 27 patients underwent diagnostic coronary arteriography and left ventriculography. Only five of these patients had evidence of either previous infarction or significant obstructive coronary artery disease as assessed with clinical or angiographic criteria, or both. Although the image defect was routinely demonstrated at rest in patients with left bundle branch block, this defect was generally normalized or less distinct with exercise in patients with no anatomic heart disease. In contrast, a larger, more distinct or new image defect with exercise correctly identified the presence of significant obstructive coronary artery disease in patients with left bundle branch block. In the clinical application of noninvasive myocardial imaging, these image defects observed at rest can lead to the false positive radionuclide interpretation of anteroseptal myocardial infarction.

Although coronary artery disease and hypertension were formerly considered the most frequent causes of left bundle branch block,[1,2] recent evidence[3] suggests that the diagnosis of coronary atherosclerosis should not be made on the basis of this electrocardiographic finding alone. Left bundle branch block has frequently been found in subjects with no anatomic cardiac disease.[3–7] In addition, recent data[6–9] suggest that patients with left bundle branch block and no angiographically demonstrable coronary artery disease have no greater morbidity or mortality than a general age-matched population. It is therefore important to determine whether left bundle branch block is associated with coronary artery disease or results from other causes. Unfortunately, in this conduction disturbance, the QRS abnormalities interfere with the recognition of most electrocardiographic patterns of infarction, and the associated ST-T wave abnormalities preclude the identification of the stress-induced changes usually considered diagnostic of coronary artery disease. Coronary angiography has usually been required to establish or exclude an atherosclerotic origin for left bundle branch block.

We have utilized noninvasive myocardial imaging with potassium-43 or rubidium-81 to evaluate more than 400 patients with coronary artery disease and have demonstrated that this technique is successful in identifying myocardial infarction and ischemia.[10–13] When patients with angina pectoris and normal ventricular conduction are studied at rest, accumulation of ^{81}Rb and ^{43}K is homogeneous and myocardial images

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are normal. During exercise-induced angina pectoris, a relative reduction in both myocardial cation uptake and tracer delivery may occur in vascular beds supplied by obstructed coronary arteries, and a regional image defect may define the ischemic vascular bed (Fig. 1). Patients with a normal heart and those with hemodynamically insignificant coronary lesions manifest normal images both at rest and during exercise (Fig. 2). In patients with remote myocardial infarction, coronary occlusion impairs isotope delivery, and radionuclide uptake is minimal in the acellular scar. The resultant image defects conform to the area of infarction with little or no change noted between rest and exercise studies in the same patient. Because of those favorable results in the study of patients with coronary artery disease, we applied this technique to the noninvasive diagnostic evaluation of 27 patients with left bundle branch block.

Materials and Methods

Case material: Myocardial imaging was performed in 27 patients with documented left bundle branch block evaluated between December 1973 and May 1975. The electrocardiographic criteria used were those of the New York Heart Association. The clinical characteristics of these patients, as well as pertinent angiographic data, are described in Table I. The patients ranged in age from 18 to 57 years; 18 patients were male and 9 were female. In eight patients the left bundle branch block was intermittent, and in three of these it was related to heart rate. Although five patients were experiencing chest pain, only one was believed to have angina pectoris. Two had sustained a well documented myocardial infarction. Four patients manifested arrhythmias, two with paroxysmal supraventricular tachycardia and two with exercise-induced ventricular ectopy. Three patients had the auscultatory and echocardiographic findings of mitral valve prolapse. The remaining 13 patients were free of any clinical suggestion of organic heart disease. No patient was known to have been hypertensive.

During the same period of time 20 patients with electrocardiographic conduction abnormalities other than left bundle branch block were similarly studied with myocardial imaging. These 20 "control" subjects included 9 patients with right bundle branch block, 8 with the Wolff-Parkinson-White preexcitation syndrome and 3 with left anterior hemiblock. No patient in this group of 20 subjects was judged clinically to have coronary artery disease.

Procedures: Sixteen of the 27 patients with left bundle branch block and the 2 with right bundle branch block and chest pain underwent selective coronary cineangiography and left ventriculography performed with use of either a brachial arteriotomy or a percutaneous femoral arterial approach. Coronary arteriograms were filmed at a rate of 60 frames/sec on 35 mm film using both the 6 and 9 inch (15 and 23 cm) fields of a variable field image intensifier. Biplane left ventricular cineangiography was performed in all patients after the intracavitary injection of 45 cc of contrast medium over 3 seconds. Angiograms were independently reviewed by three of us.

All 47 patients were evaluated at rest and after exercise with noninvasive myocardial imaging using either rubidium-81 or potassium-43 as the radioactive tracer. With use of a graded maximal treadmill protocol, patients exercised to an end point of fatigue or well established chest pain. At this time, 1.0 mCi

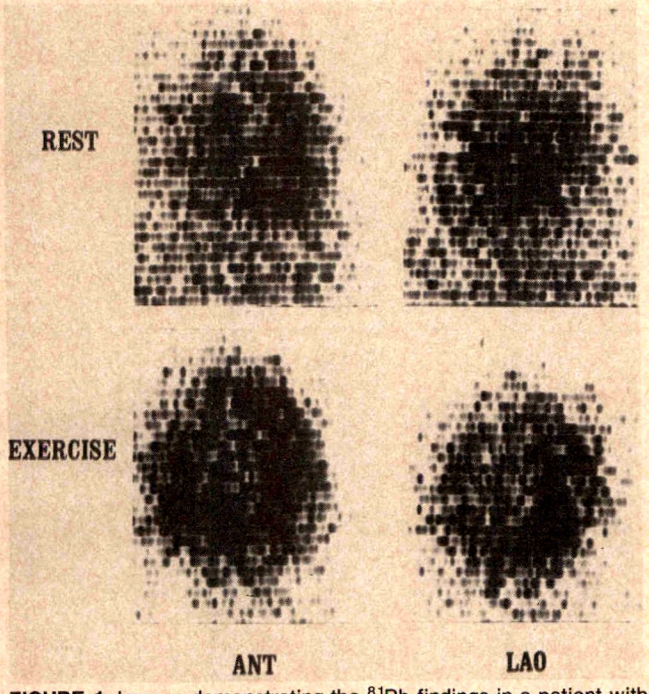


FIGURE 1. Images demonstrating the ^{81}Rb findings in a patient with angina pectoris resulting from an isolated 90 percent obstruction of the left anterior descending artery. The images obtained at rest (**upper panels**) are normal, but those after exercise to angina pectoris (**lower panels**) demonstrate reduced tracer activity in the anteroseptal region in the left anterior oblique (LAO) projection. This defect is not defined in the anterior (ANT) projection. This patient had no electrocardiographic conduction disturbance.

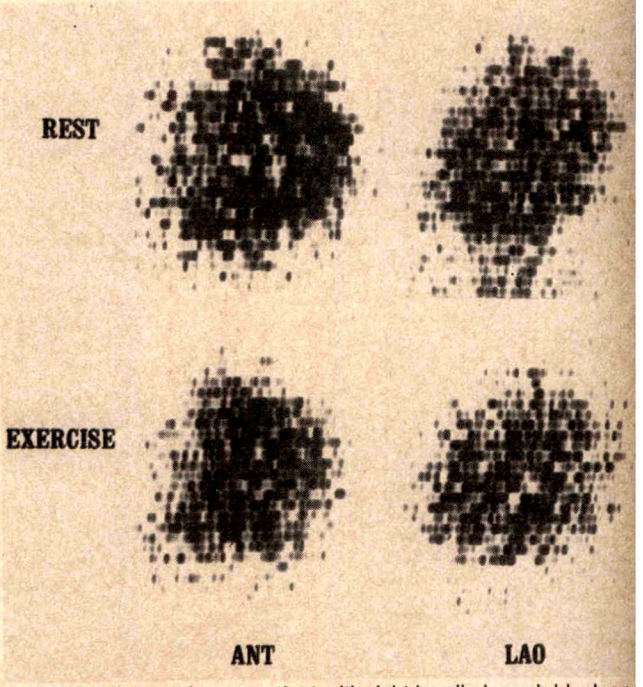


FIGURE 2. Images from a patient with right bundle branch block and angiographically normal coronary arteries demonstrate a homogeneous distribution of ^{81}Rb throughout the myocardium. The images are normal both at rest and during exercise. Abbreviations as in Figure 1.

of ^{43}K or 2.0 mCi of ^{81}Rb was injected intravenously and exercise was continued for an additional 30 to 45 seconds. The patients were then promptly taken to the adjacent nuclear medicine laboratory where duplicate images were obtained in the anterior and 45° left anterior oblique positions using a rectilinear scanner (Picker Magnascanner 500 with a 5 inch [12.5 cm] crystal) and both 3 and 5 inch (7.5 and 12.5 cm) focused high energy collimators. Images were obtained at rest 3 to 6 days later after 12 to 14 hours of fasting and 10 minutes of standing in the erect position to reduce gastrointestinal and hepatic tracer uptake. The resultant images were initially interpreted by at least two of us who were not present at the time of imaging and were not aware of the patients' clinical diagnosis or laboratory findings.

In addition, four patients with left bundle branch block and angiographically normal coronary arteries were studied with myocardial perfusion imaging using technetium-99m–labeled particles injected directly into the coronary circulation according to the technique of Ashburn et al.[14] The bolus injection of particles immediately followed an injection of 0.5 to 1.0 cc of contrast material to ensure an accurate intracoronary delivery of tracer.

Results

Coronary arteriography: Of the 16 patients with left bundle branch block subjected to selective coronary angiography, 11 presented entirely normal coronary arterial and left ventricular anatomy. Two patients with left bundle branch block and no historic or laboratory evidence of cardiovascular disease had inconsequential angiographic evidence of nonobstructive coronary atherosclerosis and normal left ventricular contraction. In the remaining three patients, angiography demonstrated severe obstructive lesions including significant obstruction of the left anterior descending coronary artery in two of the three. Of these patients one was asymptomatic, one manifested classic angina pectoris, and the third manifested paroxysmal ventricular tachycardia during exercise. None of the three had evidence of myocardial infarction. Findings were normal in the two patients with right bundle branch block studied with selective coronary angiography and left ventriculography.

Myocardial imaging: In 25 of the 27 patients with left bundle branch block, myocardial imaging with ^{43}K or ^{81}Rb both at rest and during exercise demonstrated decreased septal cation uptake consistent with anteroseptal myocardial infarction. The abnormality was present irrespective of the presence or absence of coronary artery disease and was prominent in the resting

TABLE I

Clinical and Angiographic Data in 27 Patients With Left Bundle Branch Block Undergoing Myocardial Imaging With ^{81}Rb and ^{43}K

Case no.	Age (yr) & Sex	ECG	Clinical Cardiovascular Status	Angiographic Findings of Arterial Obstruction
1	47F	Int LBBB	Normal	. . .
2	31M	Int LBBB	Normal	None
3	46F	LBBB	Mitral valve prolapse	None
4	39M	Int LBBB	Exercise-induced ventricular tachycardia	80% LAD
5	57M	LBBB, Q waves in lateral leads	Postmyocardial infarction	. . .
6	52M	LBBB	Normal	90% LCA; 50% LAD
7	26F	Int LBBB	Normal	. . .
8	39M	LBBB	Normal	None
9	44M	LBBB, long P-R interval	Postmyocardial infarction	. . .
10	37M	LBBB	Normal	50% LCA; 30% LAD
11	48F	LBBB	Mitral valve prolapse; PAT	None
12	42M	LBBB	Mitral valve prolapse; PVCs	None
13	39M	LBBB	Normal	. . .
14	35F	LBBB	Normal	. . .
15	38M	LBBB	Normal	None
16	55M	LBBB	Angina pectoris	90% LAD; 75% LCA; 85% RCA
17	42F	LBBB	Normal	None
18	50M	LBBB, long P-R interval	Normal	None
19	35M	Int LBBB	Normal	None
20	18M	Int LBBB	Paroxysmal atrial fibrillation	. . .
21	25M	LBBB	Normal	None
22	46M	Int LBBB	Normal	50% obst of 1st diagonal branch of LAD
23	44F	LBBB	Normal	. . .
24	33M	LBBB	Normal	. . .
25	39F	LBBB	Normal	. . .
26	50M	Int LBBB	Normal	None
27	49F	LBBB	Normal	. . .

Int = intermittent; LAD = left anterior descending coronary artery; LBBB = nonintermittent left bundle branch block; LCA = left circumflex coronary artery; PAT = paroxysmal atrial tachycardia; PVCs = premature ventricular contractions; RCA = right coronary artery.

image of all 25 patients. In subjects with intermittent or heart rate-related left bundle branch block, these image defects were demonstrated whether or not the electrocardiographic conduction disturbance was present at the time of study (Fig. 3). All 11 patients with angiographically normal coronary arteries and 7 pa tients without clinical evidence of coronary artery dis ease manifested the typical imaging pattern of antero septal defect at rest. Exercise imaging in these 1 subjects resulted in a normal image in 6, an equivoca image in 7 and an abnormal (but less well defined tha the resting) image in 5 (Fig. 4). Imaging in Patient yielded equivocal results at rest and normal results wit exercise; results in Patient 20 were normal both at res and with exercise. These were the only two subject whose resting study did not reveal an anteroseptal de fect.

The two asymptomatic patients who had left bundl branch block in conjunction with an anterior myocardia infarction did not undergo coronary angiography. Eac demonstrated the typical image defect associated wit an anterior myocardial scar but also seen in patient with left bundle branch block in the absence of infarc tion. In both patients the image defect was more distinc during exercise, but the area of the defect was no changed significantly from that observed at rest (Fig 5).

Three patients with left bundle branch block wit severe obstructive coronary artery disease without prior myocardial infarction demonstrated the usua image defects of left bundle branch block at rest. Wit exercise, Patient 4, who had significant obstructiv disease of the left anterior descending coronary artery manifested increased area and clearer definition of th anteroseptal image defect. Patient 6, who had signifi cant obstructive disease of the circumflex marginal ar tery, manifested a posterolateral defect with exercise whereas the high septal defect seen at rest was no longe

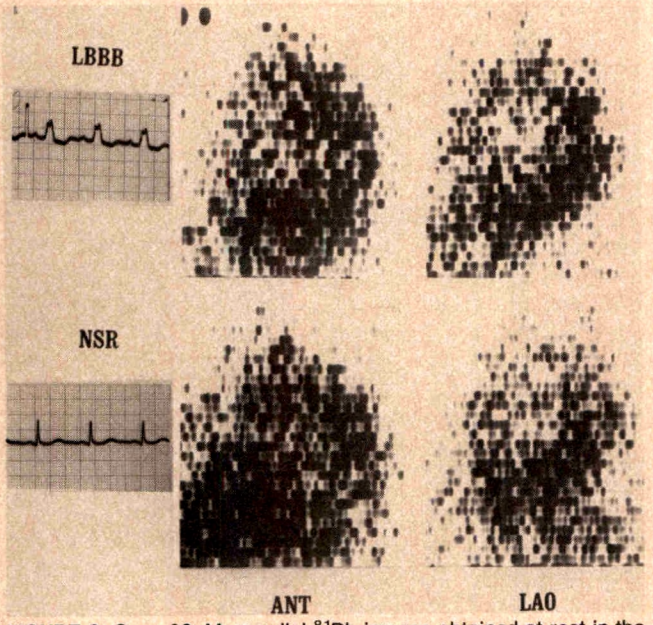


FIGURE 3. Case 26. Myocardial ^{81}Rb images obtained at rest in the anterior (ANT) and left anterior oblique (LAO) projections during left bundle branch block (LBBB) (**upper panels**) and normal conduction (NSR) (**lower panels**). The same anteroseptal defect is noted whether or not the conduction disturbance is present.

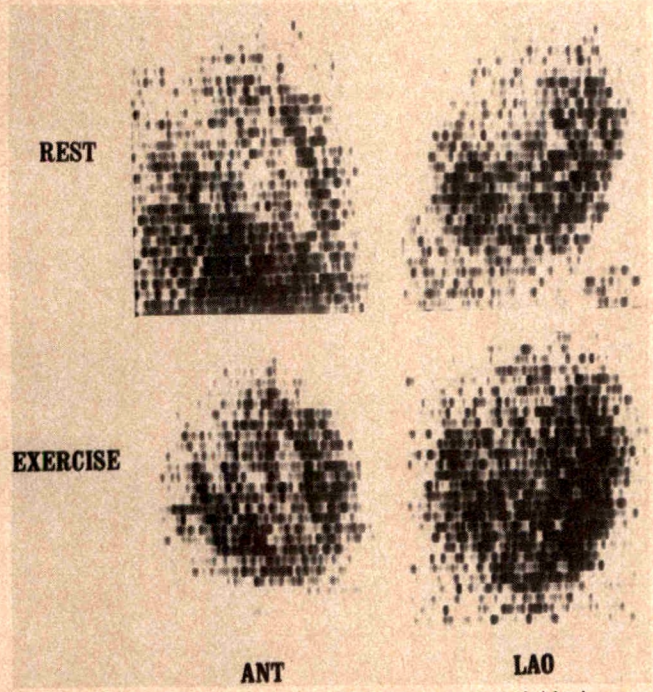


FIGURE 4. Case 11. In a patient with left bundle branch block, myocardial scans in the anterior (ANT) and left anterior oblique (LAO) projections utilizing ^{43}K demonstrate the typical anteroseptal defect associated with this conduction disturbance. The defect is more prominent at rest than during exercise.

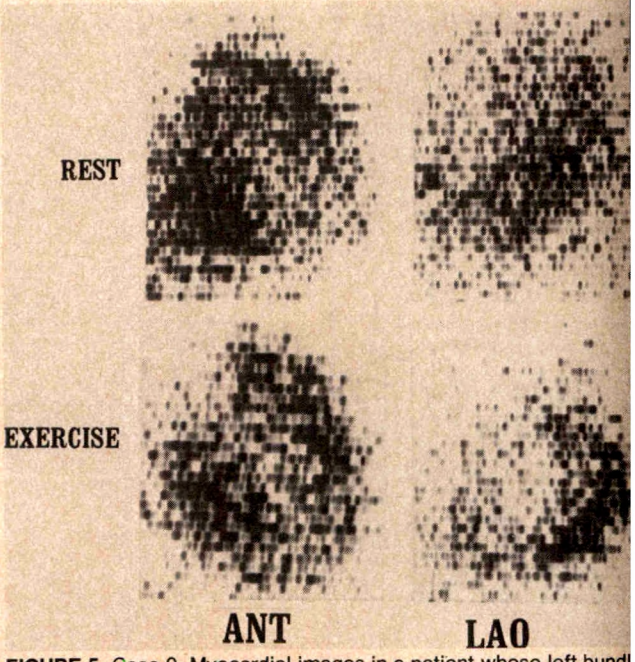
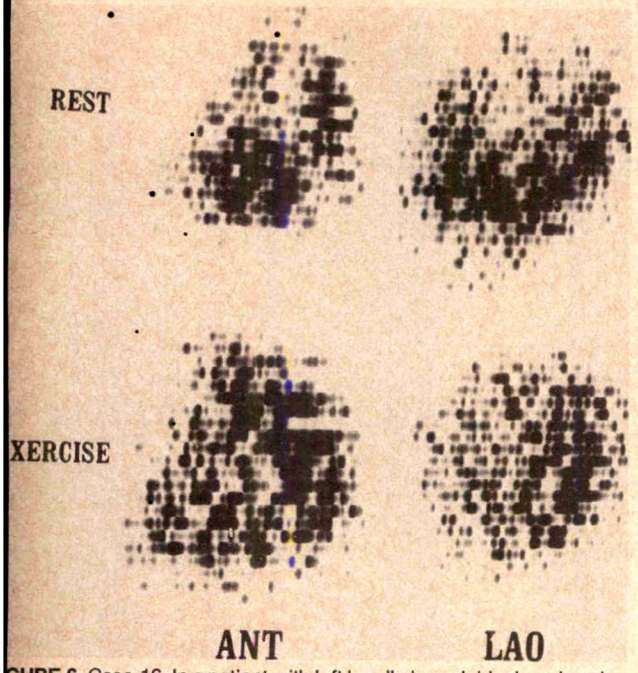


FIGURE 5. Case 9. Myocardial images in a patient whose left bundl branch block had developed in conjunction with a remote (anterio myocardial infarction. As in patients with myocardial infarction b without left bundle branch block, the defect observed at rest is mor clearly defined with exercise. Abbreviations as in Figure 4.

entified. In Patient 16, who had three vessel coronary rtery disease, exercise images demonstrated an exnsive anteroseptal defect as well as an inferior defect. nly a small anteroseptal defect had been evident at st (Fig. 6). Two asymptomatic patients with hemoynamically insignificant coronary artery disease by ngiography (luminal obstruction less than 50 percent) lso manifested an anteroseptal defect at rest that was ss evident with exercise; this pattern was similar to ndings in patients with left bundle branch block and ormal coronary arteries. One of these latter patients underwent postmortem examination after death from a head injury. Meticulous gross and microscopic examination of the heart revealed a normal interventricular septum with no evidence of circulatory, microcirculatory or fibrotic disease sufficient to cause either the conduction abnormality or the image defect.

All four patients with left bundle branch block and angiographically normal coronary arteries who underwent imaging after selective right and left intracoronary injections of ^{99m}Tc–labeled microspheres demonstrated a homogeneous distribution of radioactive particles throughout the septal myocardium; in contrast, abnormal anteroseptal uptake was noted when ^{81}Rb or ^{43}K was used for imaging studies in these same patients (Fig. 7). The 20 patients with conduction disturbances other than left bundle branch block (right bundle branch block, Wolff-Parkinson-White syndrome, left anterior hemiblock) had normal images at rest and with exercise when studied noninvasively with rubidium-81 or potassium-43 (Fig. 2).



GURE 6. Case 16. In a patient with left bundle branch block and angina ctoris myocardial images obtained at rest show the anteroseptal fect typical of left bundle branch block; with exercise to angina ctoris an additional inferior wall defect is observed. These scans monstrate how significant coronary artery disease can be identified the presence of the image defect associated with left bundle branch ck. Abbreviations as in Figure 4.

Discussion

Etiology of left bundle branch block: The main causes of left bundle branch block have been reported to be coronary artery disease, hypertension, valvular heart disease and cardiomyopathy.[1,2,6,7,15] In addition, congenital heart disease,[2] a "primary" sclerodegenerative process,[16–18] myocarditis[15] and congenital left bundle branch block[19,20] have been documented.

The early reports[1,2] on the etiology of left bundle branch block indicated that 35 to 68 percent of patients had arteriosclerotic heart disease, but several early case reports[3–5] also documented the occurrence of left bundle branch block in patients without heart disease. In addition, pathologic studies[16–18] in patients with left bundle branch block revealed localized fibrosis of bundle branches in the absence of obstructive coronary artery disease. Lewis et al.[6] reported that 8 of 12 patients with left bundle branch block had normal coronary angiograms. Haft et al.[7] noted that angiographic studies in 24 patients with left bundle branch block revealed that 7 had severe coronary disease but the re-

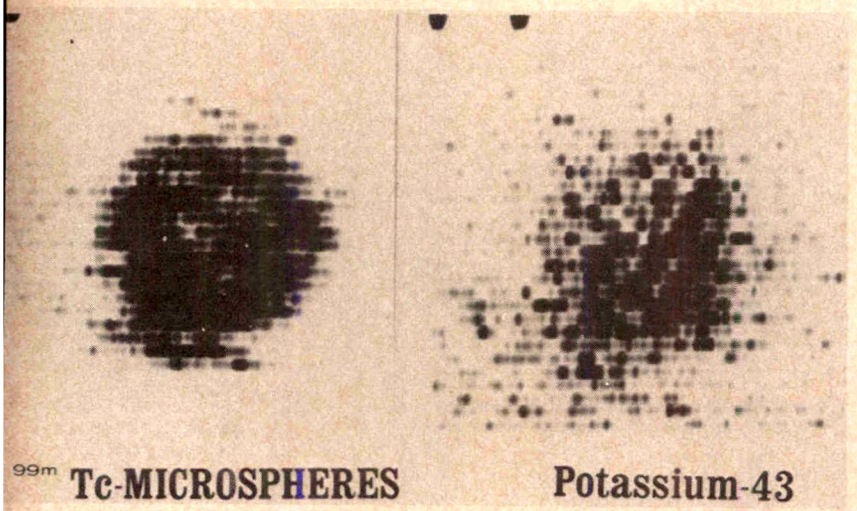


FIGURE 7. Case 18. This patient with left bundle branch block and angiographically normal coronary arteries underwent imaging after an intracoronary injection of ^{99m}Tc–labeled microspheres. A microsphere scan in the left anterior oblique projection (**left panel**) is compared with a scanner image in the same projection obtained noninvasively with ^{43}K.

maining 17 had normal coronary arteries. In addition, the prognosis of patients with left bundle branch block without demonstrable cardiovascular disease has been shown to be excellent in the work of Lewis et al.[6] and other epidemiologic studies.[1,2,8,9] Although the transient and fixed forms of left bundle branch block have been thought to have identical causes, in the study of Lewis et al. half of the patients with transient block had significant coronary disease and half did not.

Eleven of our 27 patients with left bundle branch block had angiographically normal coronary arteries, and 22 had no clinical evidence of significant coronary atherosclerosis. Although 3 of the 27 were diagnosed clinically as having mitral valve prolapse, none had rheumatic valvular heart disease or congenital heart disease and none had a history to support a diagnosis of hypertension or myocarditis. The presence of any significant degree of cardiomyopathy was precluded by the absence of X-ray evidence for left ventricular hypertrophy, the lack of clinical data to suggest cardiac decompensation and normal left ventricular performance by left ventricular end-diastolic pressure measurements and angiography, when these studies were performed. The pathologic examination of the one patient studied at autopsy revealed no small vessel disease of the left ventricle or fibrotic replacement of the myocardium.

Image defects in presence of left bundle branch block and effect of exercise: Regardless of the presence or absence of coronary artery disease, patients with left bundle branch block demonstrated an image defect at rest similar to that seen in patients with anterior myocardial infarction. Although the definition of this defect was variable, conduction abnormalities other than left bundle branch block did not demonstrate regional image defects. Thus, left bundle branch block must be added to the list of conditions that can produce false positive myocardial images.

Of equal clinical relevance is that comparison of the rest and exercise images permitted one to identify the presence of significant obstructive coronary artery disease in patients with left bundle branch block. There was a clear increase in definition of the defect with exercise imaging in patients with left bundle branch block and obstructive coronary artery disease. In addition, patients with left bundle branch block with significantly obstructed coronary arteries supplying noninfarcted vascular beds demonstrated an increase in the defect area appropriate to the distribution of the obstructed vessel. Images obtained in patients with left bundle branch block without coronary obstructive disease typically showed an abnormal septal uptake of tracer at rest that was less well defined or even normal with exercise. To date we have seen this tendency for an image defect observed at rest to normalize with exercise only in patients with left bundle branch block and normal coronary arteries.

Correlation with intracoronary tracer studies: Comparative myocardial imaging with intracoronary tracer-labeled particles and intravenously administered ^{81}Rb and ^{43}K has demonstrated excellent correlation of these techniques in identifying patients with normal and abnormal coronary circulation. Although performed in only four of the patients with normal coronary arteries and left bundle branch block, imaging after selective right and left intracoronary injections of ^{99m}Tc–labeled microspheres demonstrated a homogeneous distribution of particles in contrast to the abnormal anteroseptal tracer uptake noted during noninvasive imaging with ^{81}Rb and ^{43}K in these same patients. The reasons for these disparate results are not evident, but further comparative study of these patients employing quantitative imaging approaches might provide further physiologic insights.

Recently, Wackers et al.[21] reported that nine patients with left bundle branch block and no evidence of acute myocardial infarction had normal scintiscans with thallium-201, whereas patients with left bundle branch block and acute myocardial infarction manifested defects that localized the region of myocardial damage. One can only speculate on the reason for normal ^{201}Tl images in patients with left bundle branch block. Differences in imaging technique may be sufficient to account for this phenomenon. Alternatively, the explanation may reside in physiologic differences between the myocardial uptake patterns of ^{201}Tl and the tracers utilized in this study.[22]

Clinical implication: Twenty-two of our 27 patients with left bundle branch block had no condition considered responsible for the conduction disturbance, and in most the disturbance would be classified as idiopathic. In performing noninvasive myocardial imaging with ^{81}Rb and ^{43}K in these patients, we found that anteroseptal image defects at rest not observed in normal subjects or in patients with other selected conduction abnormalities are routinely demonstrable regardless of the presence or absence of organic heart disease. These image defects can lead to the false positive interpretation of anteroseptal myocardial infarction, and only the demonstration of larger or more distinct regions of reduced tracer uptake with exercise can correctly identify the presence of obstructive coronary artery disease.

Acknowledgment

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Electrophysiologic Effects of Atropine on Human Sinus Node and Atrium

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Electrophysiologic studies were conducted in 17 patients without apparent sinus node disease before and after intravenous administration of 1 to 2 mg of atropine. Mean values in milliseconds (± standard error of the mean) before and after administration of atropine were as follows: sinus cycle length 846 ± 26.4 versus 647 ± 20.0 ($P < 0.001$); sinus nodal recovery time 1,029 ± 37 versus 774 ± 36 ($P < 0.001$); mean calculated sinoatrial (S-A) conduction time 103 ± 5.7 versus 58 ± 3.9 ($P < 0.001$); mean P-A interval 34 ± 1.5 msec versus 31 ± 1.5 ($P < 0.05$); mean atrial effective and functional refractory periods during sinus rhythm 285 ± 11.3 versus 238 ± 7.9 and 331 ± 11.6 versus 280 ± 8.6, respectively ($P < 0.001$ for both); mean atrial effective and functional refractory periods measured at equivalent driven cycle length 239 ± 7.7 versus 213 ± 7.4 and 277 ± 11.4 versus 245 ± 9.5, respectively ($P < 0.001$ for both).

In conclusion, atropine shortened sinus cycle length, sinus nodal recovery time and calculated S-A conduction time. The shortening of atrial refractory periods with atropine implies that vagotonia prolongs atrial refractoriness in man.

It is widely believed, primarily on the basis of previous animal experimentation, that vagotonia facilitates and atropine depresses intraatrial conduction in man.[1–5] There are few studies in man either confirming or negating these hypotheses.[6,7] Intracardiac electrode catheter techniques utilizing atrial stimulation allow precise evaluation of human sinus nodal function and intraatrial conduction.[8] Recent studies[6,7,9] have described effects of atropine on only selected aspects of sinus or atrial function in small numbers of patients with and without sinus or atrial disease.

In this study, we systematically evaluated the effects of atropine on sinus and atrial properties in patients without apparent sinus node or atrial disease. As expected, there was an increase in sinus rate, a decrease in sinus recovery time and shortening of calculated sinoatrial (S-A) conduction time. There was also facilitation of intraatrial conduction as manifested by decreases in atrial effective and functional refractory periods, an unanticipated result.

Material and Methods

Patients: Seventeen patients undergoing electrophysiologic studies were studied. Eight patients had normal electrocardiograms with no evidence of conduction disturbance and nine had intraventricular conduction defects. None of these patients had documented or suspected sinus node disease. Specifically, no patient had documented sinus bradycardia, S-A block or sinus arrest. All patients had normal sinus recovery time (less than 1,680 msec), normal calculated S-A conduction time (less than 152 msec), normal P-A interval (less than 45 msec) and normal atrial effective and functional refractory periods (less than 350 and 400 msec, respectively).[8,10,11] In addition, no patient had paroxysmal tachycardia during the electrophysiologic studies.

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TABLE I

Electrophysiologic Effects of Atropine on the Sinus Node and Atrium in Individual Patients (all measurements in msec)

Case no.	Sinus Cycle Length		SRT		Calculated SACT		P-A Interval		Refractory Periods: Sinus Rhythm AERP		Sinus Rhythm AFRP		Driving at Identical Cycle Lengths: Cycle Length	Driving AERP		Driving AFRP	
	B	A	B	A	B	A	B	A	B	A	B	A		B	A	B	A
1	970	690	1410	1190	70	45	36	40	310	260	330	280	600	300	250	380	330
2	940	670	1180	740	140	85	43	41	280	230	330	280	550	240	230	270	260
3	910	750	1150	810	100	45	27	30	350	290	400	300	470	210	150	320	220
4	870	670	1018	960	85	43	36	29	320	290	370	330	550	280	250	310	290
5	990	675	1060	780	90	50	45	40	350	270	360	300	550	280	260	310	270
6	830	760	1040	840	115	60	29	18	270	230	300	260	500	250	210	270	230
7	730	660	1000	750	140	90	33	23	350	290	400	320	500	240	210	250	240
8	850	630	970	720	115	60	29	27	250	200	310	270	500	240	200	270	220
9	985	535	1120	630	75	40	19	24	280	230	330	260	500	240	225	280	270
10	780	550	860	660	105	55	40	36	250	230	300	250	500	250	230	280	260
11	920	730	1120	820	113	79	33	31	250	230	340	330	550	220	180	230	200
12	920	780	980	880	80	43	28	27	270	240	330	320	500	170	170	190	180
13	750	640	950	730	100	46	35	30	210	180	220	190	500	210	200	240	210
14	710	600	950	750	80	55	31	30	280	200	310	250	460	220	210	250	240
15	760	545	800	640	80	45	35	34	350	240	400	270	500	240	200	250	220
16	610	500	760	500	140	80	32	29	210	210	260	260	...	...	...	...	...
17	860	620	1130	750	125	70	40	40	260	230	340	290	500	240	230	330	280

A = after administration of atropine; AERP = atrial effective refractory period; AFRP = atrial functional refractory period; B = before administration of atropine; SACT = calculated sinoatrial conduction time; SRT = sinus nodal recovery time.

The group consisted of 16 men and 1 woman aged 34 to 77 years (mean ± standard error of the mean 55 ± 2.8 years). All had sinus rhythm and a normal P-R interval, and none received cardiac medication within 48 hours of the electrophysiologic study.

Protocol: Informed written consent was obtained from all subjects. His bundle electrograms were recorded using previously described catheter techniques.[10] A quadripolar catheter was positioned at the high right atrium near the vicinity of the sinus node for atrial pacing (two poles) and for recording high right atrial electrograms (two poles). Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-20 Electronics for Medicine) at paper speeds of 100 and 200 mm/sec. Simultaneous electrocardiographic leads I, II, III and V_1 were also recorded. The P-A interval was measured from the onset of the P wave to the first rapid deflection of the low right atrial electrogram recorded from the His bundle catheter, reflecting conduction time from the high to the low right atrium.[10] If the onset of the P wave could not be well delineated, the onset of the high right atrial electrogram was utilized. Measurements of the P-A interval were made at a paper speed of 200 mm/sec and reflect the average of 10 consecutive beats.

Atrial pacing was performed at increasing rates. Sinus nodal recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at a rate of 130/min.[10] Three sinus recovery times were determined and then averaged for each patient. Atrial effective and functional refractory periods were measured with the atrial extrastimulus (A_2) technique during sinus rhythm as previously described.[11]

The following definitions were used in regard to atrial refractory periods:

A_1 was the atrial electrogram of spontaneous sinus or driven beats (S_1), whereas A_2 was the atrial electrogram in response to the extrastimulus (S_2). The atrial effective refractory period was the longest S_1–S_2 interval at which S_2 did not result in atrial capture. The atrial functional refractory period was the shortest attainable propagated A_1–A_2 interval. In 16 patients, an atrial driven cycle length (from 460 to 600 msec) was also utilized so that refractory periods could be measured at identical cycle lengths before and after administration of atropine.

Sinus nodal responses to atrial extrastimuli (S_2) were categorized into four types by noting the occurrence of the first spontaneous sinus beat (A_3) after A_2.[8] These responses were defined as follows:

1. *Nonreset due to sinus interference:* when A_3 occurred at an A_2–A_3 interval longer than the spontaneous sinus cycle (A_1–A_1) and when A_1–A_3 equaled 2 × A_1–A_1 (Zone 1 response).

2. *Sinus reset:* when the A_2–A_3 interval was either equal to

TABLE II

Summary of Electrophysiologic Findings Before and After Administration of Atropine (all measurements in msec)

	Patients (no.)	State	Mean ± SEM	P Value
Sinus cycle length	17	B	846 ± 26.4	<0.001
		A	647 ± 20.0	
SRT	17	B	1029 ± 37	<0.001
		A	774 ± 36	
SACT	17	B	103 ± 5.7	<0.001
		A	58 ± 3.9	
P-A interval	17	B	34 ± 1.5	<0.05
		A	31 ± 1.5	
Atrial ERP (NSR)	17	B	285 ± 11.3	<0.001
		A	238 ± 7.9	
Atrial FRP (NSR)	17	B	331 ± 11.6	<0.001
		A	280 ± 8.6	
Atrial ERP (during atrial driving)	16	B	239 ± 7.7	<0.001
		A	213 ± 7.4	
Atrial FRP (during atrial driving)	16	B	277 ± 11.4	<0.001
		A	245 ± 9.5	

A = after administration of atropine; B = before administration of atropine; ERP = effective refractory period; FRP = functional refractory period; NSR = normal sinus rhythm; P = probability; SACT = sinoatrial conduction time; SEM = standard error of the mean; SRT = sinus recovery time.

or more than A_1–A_1 and when A_1–A_3 was less than twice A_1–A_1 (Zone 2 response).

3. *Sinus interpolation:* when the A_2–A_3 interval was less than A_1–A_1 and when A_1–A_3 was either equal to A_1–A_1 (complete interpolation) or more than A_1–A_1 (incomplete interpolation).

4. *Sinus echoes:* when the A_1–A_3 interval was less than A_1–A_1 and when the P wave configuration of A_3 approximated that of the normal P wave with a high to low sequence of atrial activation.

Data presentation and analysis were facilitated by plotting A_1–A_3 responses against A_1–A_2 coupling intervals.[8]

Each patient was categorized as to whether he had these zones of nonreset because of interference, reset, interpolation or echoes. In each patient, a zone could be defined by its longest and shortest A_1–A_2 coupling interval and in terms of its absolute duration. When all patients with a given zone were considered, the zone could be described in terms of both its mean longest and shortest A_1–A_2 coupling intervals and its mean absolute duration.

Sinoatrial conduction time was calculated utilizing the atrial extrastimulus technique.[8,12] For each patient, this value was obtained by measuring the difference between the A_2–A_3 and A_1–A_1 intervals during reset and dividing by 2. A mean sinoatrial conduction time was calculated for each patient using all reset responses.

Atropine was administered intravenously (a dose of 2 mg to patients less than 60 years of age, and of 1 mg to patients 60 years and over) after control recordings were obtained. Measurements were initiated 10 minutes after administration of atropine. Statistical analysis of data was performed using Student's t test for paired values.

Results

Intraatrial conduction (Tables I and II): The mean P-A interval (± standard error of the mean) was 34 ± 1.5 msec before and 31 ± 1.5 msec after administration of atropine (P <0.05). Atrial effective and functional refractory periods were measured in all patients during sinus rhythm. The mean atrial effective refractory period was 285 ± 11.3 msec before versus 238 ± 7.9 msec after atropine (P <0.001). The mean atrial functional refractory period was 331 ± 11.6 msec before versus 280 ± 8.6 msec after atropine (P <0.001). The mean atrial effective refractory period at identical driven cycle lengths in 16 patients was significantly reduced from 239 ± 7.7 msec to 213 ± 7.4 msec after administration of atropine (P <0.001). (Fig. 1). The mean functional refractory period of the atrium was also shortened from 277 ± 11.4 to 245 ± 9.5 msec with atropine (P <0.001). The P wave configuration did not change after administration of atropine.

Effect on sinus node (Tables I and II): The mean cycle length during sinus rhythm was 846 ± 26.4 msec before and 647 ± 20.0 msec after administration of atropine (P <0.001). Sinus nodal recovery times significantly shortened after atropine. The mean sinus nodal

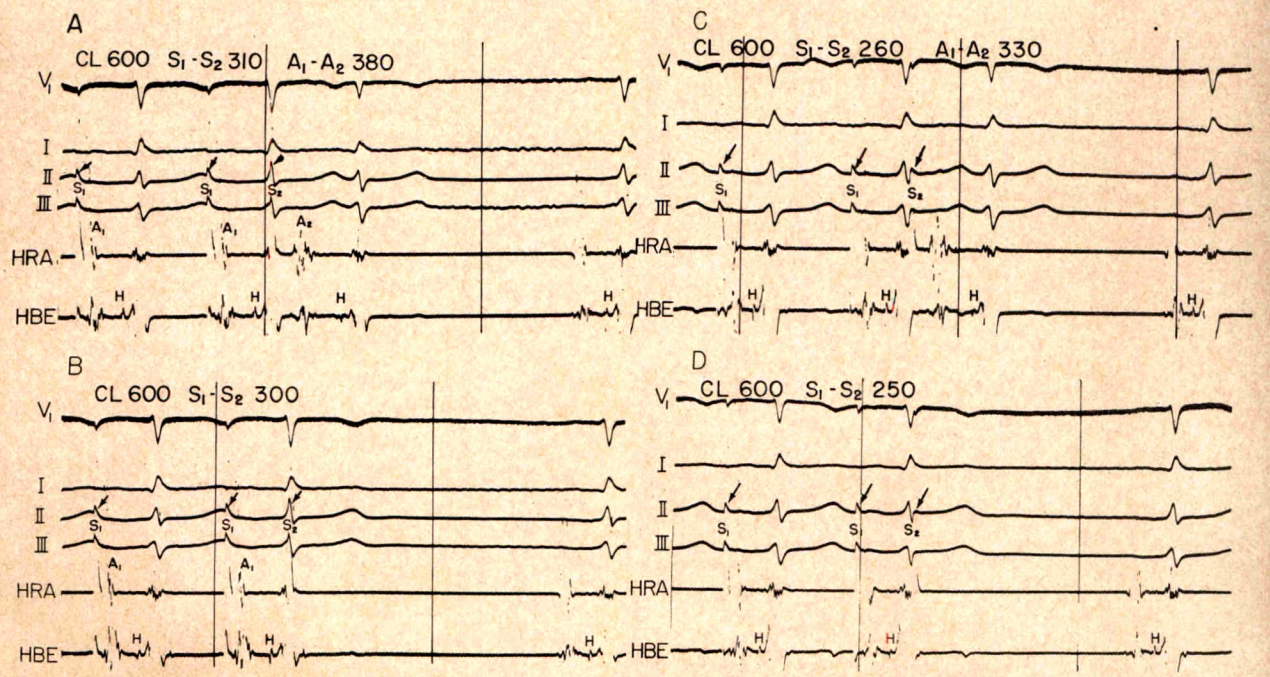


FIGURE 1. Case 1. Measurements of atrial refractory periods before and after administration of atropine. Shown are electrocardiographic leads V_1, I, II and III, a bipolar intracardiac high right atrial electrogram (HRA) and a His bundle electrogram (HBE). Paper speed is 100 mm/sec and time lines are at 1 second intervals. The cycle length (CL) of the basic drive (S_1) is 600 msec and the extrastimulus and atrial coupling intervals (S_1–S_2 and A_1–A_2, respectively) are listed at the top of each panel. A_1 is the atrial electrogram induced by S_1, and A_2 is the atrial electrogram of the extrastimulus S_2. **A** and **B** are control recordings; **C** and **D** were obtained after administration of atropine. **A,** at a coupling interval of 310 msec, S_2 is conducted to the atrium. The A_1–A_2 interval is 380 msec and is the shortest attainable A_1–A_2 interval, thereby defining the functional refractory period of the atrium before the administration of atropine. **B,** S_2 fails to capture the atrium at a coupling interval of 300 msec, thereby defining the effective refractory period of the atrium before administration of atropine. **C,** at a coupling interval of 260 msec, S_2 is conducted to the atrium. The A_1–A_2 coupling interval is 330 msec and is the shortest attainable A_1–A_2 interval, thereby defining the functional refractory period of the atrium after administration of atropine. **D,** S_2 fails to capture the atrium at a coupling interval of 250 msec, thereby defining the effective refractory period of the atrium after administration of atropine.

recovery time was 1,029 ± 37 msec before and 774 ± 36 msec after atropine (P <0.001).

A zone of nonreset due to interference was defined in all patients both before and after administration of atropine (Fig. 2). The mean zone of interference ranged from 840 msec (outer limit) to 609 msec (inner limit) with an absolute duration of 231 msec at a mean sinus cycle length of 846 msec before administration of atropine. There was significant shortening of this zone after administration of atropine to an outer limit of 640 msec and an inner limit of 510 msec with an absolute duration of 130 msec at a mean cycle length of 647 msec (P <0.05) (Fig. 2). This zone accounted for the last 27 percent of the sinus cycle length before and 20 percent of the sinus cycle length after administration of atropine (P <0.05).

A zone of sinus reset was present in all patients both before and after administration of atropine (Fig. 2). During the control state; the mean zone of reset in these patients ranged from 599 msec (outer limit) to 336 msec (inner limit), with an absolute duration of 263 msec. There was no significant effect of atropine on the sinus reset zone. The mean zone of reset after administration of atropine was between 500 (outer limit) and 282 msec (inner limit) with an absolute duration of 218 msec (difference not significant). The zone of reset accounted for 31 percent of sinus cycle length before and 33 percent after atropine (difference not significant).

Zones of sinus interpolation were present in two patients during the control state. In both, atropine abolished interpolation responses. No patient manifested sinus interpolation after administration of atropine.

Sinus echoes were present in one patient before administration of atropine. Atropine abolished the echo responses in this patient. No patient manifested echoes after atropine.

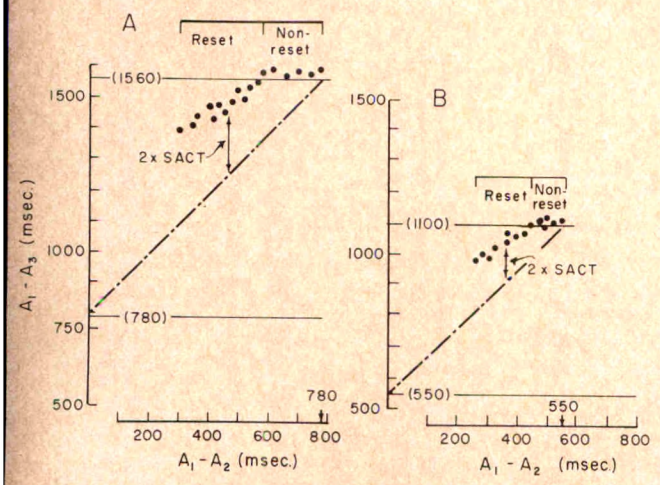


FIGURE 2. Case 10. Graphic representation of sinus nodal responses and zones to extrastimuli during sinus rhythm. A_1–A_3 intervals are plotted on the ordinate as a function of the test cycles (A_1–A_2) on the abscissa. **A,** before atropine. The sinus cycle is 780 msec. The zone of nonreset due to interference ranges from 780 to 570 msec, and the zone of reset from 560 to 300 msec. The S-A conduction time (SACT) is 105 msec. **B,** after atropine. The sinus cycle is 550 msec. The zone of nonreset ranges from 550 to 440 msec, and the zone of reset from 430 and 250 msec. The S-A conduction time is 55 msec.

Sinoatrial (S-A) conduction time was calculated both before and after administration of atropine (Fig. 2 and 3). The mean calculated S-A conduction time was 103 ± 5.7 msec before and 58 ± 3.9 msec after atropine (P <0.001).

Discussion

Effects of vagal stimulation and atropine on atrial electrophysiology: Most previous experimental studies were designed to evaluate the effect of vagal stimulation or infusion of acetylcholine on atrial refractoriness and to study the interference with these effects by atropine.[1–3] Andrus and Carter[1] demonstrated shortening of atrial refractory periods secondary to vagal stimulation in intact canine hearts and noted that this decrease could be blocked by atropine. Intravenous administration of atropine without vagal stimulation (but with intact vagi) caused a 20 percent increase in the atrial effective refractory period. Studies in the isolated cat auricle by Dipalma and Mascatello[2] revealed that atropine could rapidly reverse the decrease in atrial refractoriness induced by acetylcholine. The same studies showed that atropine without acetylcholine increased atrial refractoriness by an average of 27 percent, thus suggesting that atropine also had direct effects on the atrium. In another experimental study, Torchiana and Angelakos[3] demonstrated antagonism between acetylcholine and atropine and reported that the latter alone had no effect on atrial refractoriness in the intact dog heart.

Information regarding the effect of atropine on atrial electrophysiologic properties in man is limited. Akhtar et al.,[6] using His bundle studies, reported variable effects of atropine on atrial refractoriness in nine patients. The atrial effective refractory periods decreased 10 to 20 msec with atropine in four patients and increased 10 msec in three; no change occurred in two. In their study, neither data on the effective refractory periods of individual patients nor statistical analyses were furnished, and the dose of atropine employed was relatively small (0.5 mg). Bissett et al.[7] demonstrated no significant effect of atropine (0.5 to 1 mg) on atrial effective refractory periods in seven patients (one with sinus node disease). Neither Akhtar et al. nor Bissett et al. reported the effect of atropine on atrial functional refractory periods. In our study, atropine (1 to 2 mg) produced a significant decrease in atrial effective and functional refractory periods both during sinus rhythm and at equivalent driven cycle lengths in 17 patients without apparent sinus node disease. This finding is in contrast to the atropine-induced increase of atrial refractoriness in animals with intact vagi, thus suggesting a possible species-specific difference. The effects of atropine demonstrated in our study imply that vagotonia in man increases atrial refractoriness.

The P-A interval, a measure of conduction from the high to the low right atrium, decreased slightly but significantly in 13 of 17 patients after administration of atropine. This observation, together with shortening of the atrial refractory periods, suggests that atropine facilitates human intraatrial conduction.

Effects of atropine on sinus nodal physiology: The effects of atropine on sinus nodal automaticity have

been well studied in both animals and man.[6,7,13–16] Atropine is known to have a positive chronotropic effect on the sinus node, and it has been suggested that this effect is due to its vagolytic properties. Our data are in agreement with these observations. Sinus nodal automaticity was enhanced, as suggested by the shortening of the sinus cycle length by 23 percent after administration of atropine. In addition, atropine decreased sinus recovery time in all patients. This finding presumably reflects both enhancement of sinus automaticity and a decrease in S-A conduction time (see later).

Information concerning the effect of atropine on S-A conduction time is limited. After preliminary studies in 15 patients with sinus bradycardia, Reiffel et al.[9] suggested that atropine decreases calculated sinoatrial conduction time. Our study confirmed their findings by demonstrating an average 43 percent decrease in calculated S-A conduction time after administration of atropine. Shortening of the cycle length with atropine cannot explain this change because the calculated S-A conduction time prolongs with a spontaneous decrease in cycle length.[17]

The method for indirect calculation of S-A conduction time has yet to be validated by direct recordings in man and it is based on the following assumptions: (1) that there is no change in sinus automaticity or a shift of the sinus pacemaker with extrastimuli, (2) that all extrastimuli during the zone of reset are able to penetrate the sinus node and reset it, and (3) that antegrade and retrograde S-A conduction times are equal. Some experimental studies in animal hearts[18] suggest that these assumptions may not be totally valid.

The zone of sinus nonreset due to interference represents a period late in atrial diastole in which impulses from elicited atrial extrastimuli collide with the outgoing sinus impulses and are thus unable to reset the sinus node.[12] This collision or interference is presumably in the perinodal tissue.[19,20] The magnitude of the zone of nonreset varies directly with S-A conduction. Prolongation of S-A conduction time would induce lengthening of the zone of interference and vice versa. Atropine caused shortening of this zone as well as a decrease in S-A conduction time. Both effects probably reflect facilitation of conduction in perinodal tissue. Atropine appeared to have a similar effect on atrial tissue and perinodal fibers despite the different electrophysiologic properties of these two tissues.[21]

The presence of sinus interpolation (unidirectional sinus entrance block) and sinus echo responses in patients suggests increased refractoriness of perinodal fibers.[8,19,20,22] Since atropine probably facilitates perinodal conduction, as suggested by shortening of S-A conduction time and the zone of interference, it is not surprising that both interpolation and echo responses were eliminated by atropine in our study.

Atropine versus ouabain effects: Most of the electrophysiologic effects of atropine on the human atrium and sinus node are opposite to those described in a recent study with ouabain.[23] In that study, ouabain prolonged S-A conduction time and atrial refractory

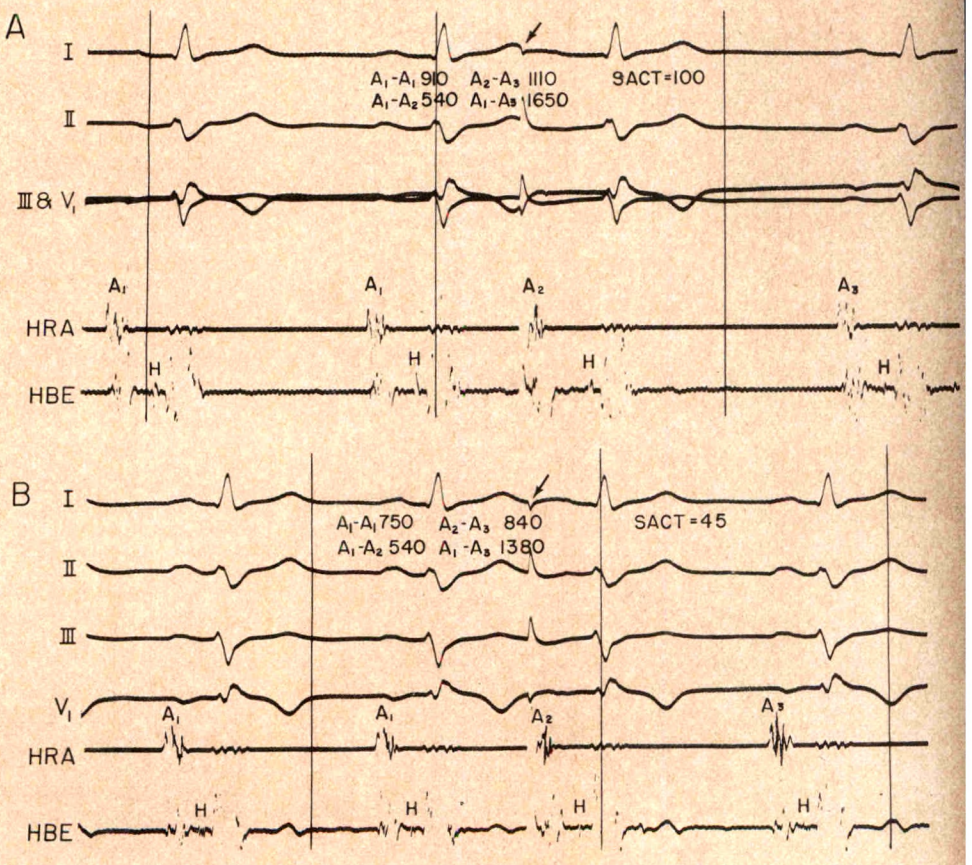


FIGURE 3. Case 3. Measurements of S-A conduction time before (**A**) and after (**B**) administration of atropine. The sinus cycle length (A_1–A_1), atrial coupling interval (A_1–A_2), return cycle length (A_2–A_3), combined coupling and return cycle length (A_1–A_3) and calculated S-A conduction time (SACT) are listed in each panel. **A,** sinus rhythm at an A_1–A_1 interval of 910 msec. At a coupling interval of 540 msec, the A_2–A_3 interval is 1110 msec, which is more than the A_1–A_1 interval, whereas the A_1–A_3 interval of 1,650 msec is less than twice the A_1–A_1 interval. The sinus node is reset by A_2. The S-A conduction time (half the difference between A_2–A_3 and A_1–A_1) is 100 msec before administration of atropine. **B,** sinus rhythm after administration of atropine with an A_1–A_1 interval of 750 msec. At a similar coupling interval of 540 msec the A_2–A_3 interval is 840 msec with reset of the sinus node. The calculated S-A conduction time is 45 msec.

periods. The opposite atropine actions suggest that the ouabain effects could be vagally mediated. In contrast, both atropine and ouabain shortened sinus nodal recovery times. However, we would postulate different mechanisms for this similar action. Because resting sinus rates were unchanged with ouabain, the abbreviation of sinus recovery time probably reflected increased refractoriness of perinodal fibers, allowing fewer driven atrial impulses to penetrate the sinus node and resulting in pseudoshortening of recovery time.[23] Atropine shortened the sinus cycle length (increased sinus rate) and S-A conduction time, suggesting that the shortening of sinus recovery time reflected both an increase in sinus automaticity and facilitation of perinodal conduction.

Clinical implications: Our study provides strong contrary evidence to the long-held view that vagotonia facilitates intraatrial conduction in man and that vagolysis has an opposite effect. Previous clinical observations[24–31] concerning the effects of digitalis, atropine and carotid sinus massage on atrial fibrillation and flutter and paroxysmal ectopic atrial tachycardia have to be reevaluated in view of these new findings. For example, the sporadic reported cases of conversion of atrial fibrillation or flutter to sinus rhythm after carotid sinus massage and the commonly observed conversion of atrial fibrillation to sinus rhythm with digitalization could be explained by prolongation of atrial refractoriness due to vagotonia.[27,32,33]

Another implication of our study in patients without apparent sinus node disease concerns the potential usefulness of atropine in patients with such disease. The facilitation of S-A conduction and improved sinus automaticity found in our patients would be beneficial to patients with sinus node disease. The effects of atropine in such patients deserve further electrophysiologic study.

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Reduction of S-T Segment Elevation With Infusion of Nitroprusside in Patients with Acute Myocardial Infarction

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The effect of infusion of sodium nitroprusside on S-T segment elevation was evaluated in 12 patients with acute anterior myocardial infarction. Precordial 35 lead S-T segment maps were obtained in each patient immediately before and 10 minutes after infusion of 53 μg/min (range 20 to 100 μg/min) of nitroprusside. The following measurements were made from each S-T map: ΣST (total S-T elevation in all leads), NST (number of leads with S-T elevation greater than 1 mm) and $\overline{ST}$ (average S-T elevation in leads with more than 1 mm elevation). After administration of nitroprusside, evidence of myocardial ischemic injury as assessed by S-T mapping decreased in association with reduction of the myocardial oxygen consumption index of pressure-time per minute. Group mean values diminished significantly for ΣST (41.7 to 28.6 mm, $P < 0.001$), NST (20.3 to 14.6, $P < 0.001$) and $\overline{ST}$ (1.6 to 1.2 mm, $P < 0.005$). Pressure-time per minute decreased from 2,690 to 2,372 mm Hg-sec/min ($P < 0.001$). Because there was no significant relation ($P > 0.05$) between reductions in S-T elevation and lower indexes of myocardial oxygen consumption it is suggested that nitroprusside may possess a separate action of augmenting regional blood flow to ischemic myocardium. Evaluation with the precordial S-T mapping technique suggested that intravenous administration of nitroprusside was associated with evidence of reduced ventricular ischemic injury in patients with acute myocardial infarction. This effect appears to be related to reduction of myocardial oxygen demand by the peripheral cardiac unloading mechanisms of nitroprusside as well as to a possible direct action of the drug in improving regional blood flow to ischemic heart muscle.

Vasodilating agents that afford dramatic reductions in cardiac afterload greatly enhance cardiac performance in patients with left ventricular dysfunction consequent to acute and chronic coronary heart disease.[1–] An important and unique feature of afterload reduction in the setting of cardiac failure is the major decline in indexes of myocardial oxygen consumption that occurs in association with improvement in cardiocirculatory variables. Although limitation of the extent of myocardial infarction has been demonstrated with sublingual[10] and intravenous[11–] administration of nitroglycerin and trimethaphan,[17] there is no clinical documentation that the extent of ischemic injury is reduced by nitroprusside, probably the most useful of the cardiac unloading agents in left ventricular failure.[7] Furthermore, it is unresolved whether ability of nitroprusside to reduce myocardial oxygen needs is offset by its potentially deleterious effect of decreasing coronary perfusion pressure. Accordingly, this investigation was carried out to quantify with precordial S-T segment mapping the effects of nitroprusside on the extent of ischemic injury in patients with acute anterior myocardial infarction.

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Methods and Material

Patients: The study population consisted of 12 patients with acute transmural anterior myocardial infarction admitted to the coronary care unit of the University of California at Davis-Sacramento Medical Center. There were nine men and three women with a mean age of 58 years (range 31 to 81 years). All patients were evaluated within 2 hours from the time of admission to the coronary care unit and within 6 hours of the time of onset of chest pain (mean 4.2 hours). Each patient had S-T segment elevation and abnormal (0.04 second or more) Q waves in at least three precordial leads of the standard 12 lead electrocardiogram. The diagnosis of myocardial infarction was made with use of the following criteria: classic history, typical serum enzyme alterations and characteristic electrocardiographic evolutionary changes. Criteria for exclusion from the investigation were systolic blood pressure of less than 100 mm Hg and uncertainty as to the time of occurrence of pain. No patient had evidence of pericarditis, ventricular aneurysm or intraventricular conduction disturbance. The nature of the study was explained to each patient and informed consent was obtained.

Hemodynamic measurements: The patients underwent right heart catheterization at the bedside in the coronary care unit with use of a no. 7 balloon-tipped flow-directed Swan-Ganz catheter and a 20 gauge Longdwell polyethylene catheter inserted into the right brachial or radial artery. Pressures were measured utilizing a Statham P23Db strain gauge. Cardiac output was measured in duplicate by the indicator-dilution technique with injection of indocyanine green dye into the pulmonary artery and sampling from the systemic arterial site utilizing a constant speed Harvard withdrawal pump and a Lyons cardiac output computer. All data were recorded on a Hewlett-Packard multichannel photographic recorder. The following hemodynamic measurements were made: heart rate (HR), phasic and mean (MAP) systemic arterial pressures, phasic and mean pulmonary arterial pressures, phasic and mean (PAW) pulmonary capillary wedge pressures and cardiac output. The following data were calculated: cardiac index (CI); stroke index (SI); stroke work index (SWI) = SI × (MAP-LVFP) × 0.0136 g·m/m^2 where LVFP = left ventricular filling pressure; total systemic vascular resistance (TSVR) = 80 × ([MAP-RA]/CO) dynes-sec-cm^{-5} where $\overline{RA}$ = mean right atrial pressure and CO = cardiac output; pressure-time per minute = MAP × ET × HR mm Hg-sec per minute where ET = ejection time determined from phasic arterial pressure.

S-T segment mapping: Immediately after control hemodynamic measurements were made, electrocardiographic recordings were obtained from a 35 lead precordial blanket (Medical Innovations, Boston, Mass.). The blanket, comprising five vertical and seven horizontal rows of electrodes, was positioned on the anterior chest with lead I in the second right intercostal space adjacent to the sternum. This position was maintained for all recordings. Electrocardiographic recordings were obtained utilizing the V lead of the standard electrocardiograph at a paper speed of 25 mm/sec. One mm of electrocardiographic excursion was standardized to correspond to 0.1 mv. The height of the S-T segment above the isoelectric line was measured for six consecutive beats in each lead and averaged. Measurement of the S-T segment was made 60 msec after the J junction of the QRS-T complex. When the J junction could not be well defined, S-T segment elevation was measured 120 msec after the initial Q or R deflection. The following data were determined from the precordial electrode blanket: sum of all S-T elevations (ΣST), number of leads with S-T elevation greater than 1 mm (NST) and average S-T elevation ($\overline{ST}$) as determined by (ΣST/NST).

Measurement of S-T segments was made by two observers without knowledge of whether the electrocardiographic recordings were obtained during the control or treatment periods, and the results were then averaged. Only leads with technically adequate recordings were measured. If a lead was not clearly recorded during both the control and nitroprusside portions of the study, it was not included in the measurements.

Nitroprusside infusion: After control data on hemodynamic variables and S-T segment maps were recorded, sodium nitroprusside was infused intravenously at an initial rate of 16 μg/min. The rate of infusion (range 20 to 100 μg/min) was individually adjusted to reduce systemic systolic arterial pressure to 100 to 115 mm Hg in 8 of the 12 patients. In four patients left ventricular filling pressures were reduced with nitroprusside to the low levels of 6 and 7 mm Hg, thus preventing use of increased doses of nitroprusside to reduce systolic pressures to 115 mm Hg. After a stable optimal rate of nitroprusside infusion had been maintained for 10 to 15 minutes, hemodynamic measurements and S-T segment recordings were repeated. No additional medications were ad-

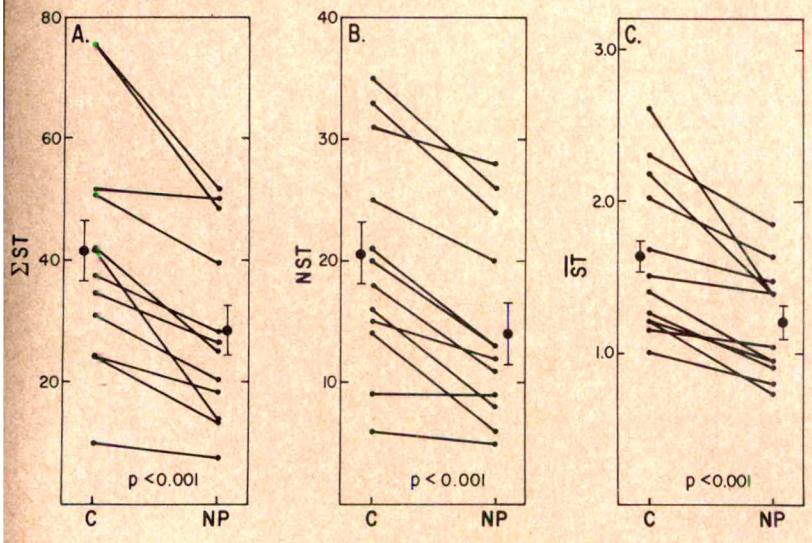


FIGURE 1. Effects of infusion of nitroprusside (NP) on sum of S-T elevation (ΣST) **(A)**, the number of precordial electrocardiographic leads with S-T elevation greater than 1 mm (NST) **(B)**, and the average S-T elevation ($\overline{ST}$) determined by (ΣST/NST) **(C)**. C = control.

ministered during or after acquisition of control data on hemodynamic variables until completion of the study protocol. Student's t test for paired data was utilized for statistical analysis.

Results

The hemodynamic responses to nitroprusside are shown in Table I. There were significant reductions ($P < 0.05$) in systolic and diastolic blood pressures, mean arterial pressure, mean pulmonary capillary wedge pressure (PAW), cardiac index (CI), total systemic vascular resistance and pressure-time per minute. There were no significant changes ($P > 0.05$) in heart rate or stroke work index (SWI). The ratios SWI/PAW and CI/PAW increased significantly during nitroprusside therapy to 1.68 ± 0.32 (mean ± standard error of the mean) to 2.95 ± 0.68 ($P < 0.005$) and 0.14 ± 0.02 to 0.25 ± 0.05 ($P < 0.01$), respectively.

Figure 1 indicates the results for the individual patients and the entire group with respect to ΣST, NST and $\overline{ST}$ before and during infusion of nitroprusside. As shown, there were significant reductions in the mean values for each of the S-T segment indexes. ΣST decreased from 41.7 ± 5.7 to 28.6 ± 4.5 mm (−31 percent, $P < 0.005$), NST from 20.3 ± 2.7 to 14.6 + 2.3 (−28 percent, $P < 0.001$) and $\overline{ST}$ from 1.62 ± 0.15 to 1.21 ± 0.10 mm (−25 percent, $P < 0.005$).

The extent of reduction in S-T elevation with nitroprusside was greatest in the patients who had the greatest initial S-T elevation. Thus, patients with ΣST greater than 40 mm in the control state had a mean reduction of 22.3 mm during infusion of nitroprusside, whereas patients with ΣST less than 40 mm had a mean reduction of only 7.4 mm ($P < 0.01$) (Fig. 2). Similarly, in the group with a control $\overline{ST}$ of 1.5 mm or greater, the reduction was 0.68 mm during nitroprusside therapy, whereas patients with $\overline{ST}$ of less than 1.5 mm before therapy had a 0.29 mm decrease during therapy.

Infusion of nitroprusside resulted in a decrease of pressure-time per minute from 2,690 ± 186 to 2,372 ± 171 mm Hg-sec min ($P < 0.001$). There was no statistically significant ($P > 0.05$) relation between reductions in the S-T segment indexes and reductions in mean systemic arterial pressure, pulmonary capillary wedge pressure or pressure-time per minute.

Discussion

Because pump failure is the leading cause of hospital death and post-hospital morbidity in patients with acute myocardial infarction and its incidence is directly related to the extent of myocardial necrosis,[18,19] the

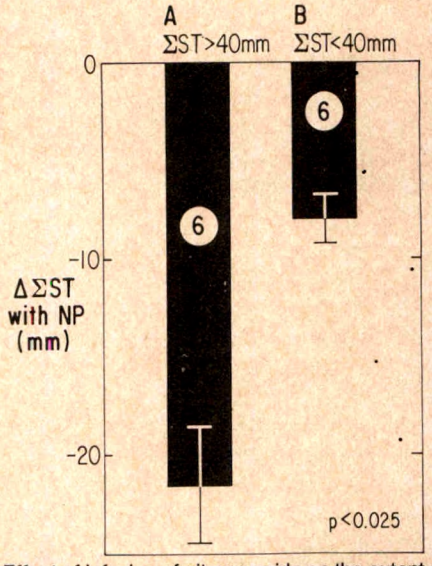


FIGURE 2. Effect of infusion of nitroprusside on the extent of reduction in S-T elevation in patients with ΣST of 40 or more mm **(A)** and less than 40 mm **(B)**.

TABLE I

Hemodynamic Responses to Nitroprusside

Case no.	Control								Nitroprusside							
	BP	MAP	HR	PAW	CI	SWI	PTM	TSVR	BP	MAP	HR	PAW	CI	SWI	PTM	TSVR
1	125/85	90	132	34	1.31	6.46	3445	2780	100/65	76	130	23	1.54	8.50	2964	2000
2	124/70	90	70	13	3.03	45.2	1890	1270	108/64	78	72	8	2.75	39.0	1685	1211
3	135/74	93	57	18	2.07	34.0	1802	2000	120/60	80	63	7	2.16	33.5	1663	1649
4	215/78	114	71	14	2.14	39.8	2590	2252	145/70	81	79	8	2.20	27.7	2112	1608
5	127/60	82	83	11	1.85	21.5	2314	1812	110/50	68	82	7	2.16	24.3	1729	1286
6	165/70	92	86	9	1.90	24.9	2453	1936	152/65	87	85	7	2.04	26.1	2366	1706
7	115/90	100	140	27	1.79	14.9	4060	2133	100/78	85	138	18	2.18	14.6	3519	1736
8	142/80	104	110	16	4.35	47.3	3318	1051	134/77	99	107	6	4.33	51.1	3178	741
9	125/70	88	95	18	2.12	21.2	2508	1617	101/61	73	96	10	1.97	18.2	2172	1483
10	148/73	100	98	22	2.00	22.5	2548	2388	107/58	76	102	14	2.32	19.2	2171	1625
11	125/65	85	100	19	1.69	15.2	2635	2537	108/60	76	101	13	1.88	15.9	2380	2040
12	120/75	90	95	21	1.31	12.8	2738	2769	103/70	80	96	13	1.36	13.0	2534	2370
Mean	139/74	94	95	18.5	2.14	25.5	2690	2045	115/65†	80†	96	11.1†	2.24*	24.3	2372†	1621†
± SEM	±8/2.4	±2.6	±7	±2	±0.24	±3.8	±186	±158	±5.2/2.3	±2.3	±6.4	±1.5	±0.22	±3.5	±171	±122

* = $P < 0.05$.
† = $P < 0.01$.
BP = blood pressure (mm Hg); CI = cardiac index (liters/min per m^2); HR = heart rate (beats/min); MAP = mean systemic arterial pressure (mm Hg); PAW = pulmonary arterial mean wedge pressure (mm Hg); PTM = pressure-time per minute (mm Hg-sec/min); SEM = standard error of the mean; SWI = stroke work index (g-m/m^2); TSVR = total systemic vascular resistance (dynes sec cm^{-5}).

ability to limit infarct size is an important clinical objective. Utilizing experimental models of acute coronary occlusion, Maroko et al.[20,21] have pioneered in the study of pharmacologic interventions that influence the extent of ischemic injury as estimated by direct epicardial electrical mapping techniques. More recently, attempts have been made to use precordial electrocardiographic mapping[10–13,22,23] in acute clinical coronary disease to extend the evaluation of specific measures to reduce the size of myocardial necrosis and ischemia.

Our investigation assessed in patients with acute anterior wall myocardial infarction the effects of infusion of sodium nitroprusside on cardiac hemodynamics and on the extent of ischemic injury as determined by precordial S-T segment mapping. This use of the potent unloading agent was prompted by previous investigations[3,7] in which nitroprusside substantially improved hemodynamic variables and concomitantly reduced principal determinants of myocardial oxygen requirements in patients with acute and chronic coronary heart disease with congestive heart failure.[3,7] Moreover, nitroprusside has been shown to reduce the extent of pacing-induced myocardial ischemia quantified by electrocardiographic and metabolic assessments in patients with coronary artery disease.[24] Additionally, experimental studies have indicated that nitroprusside improves the mechanical performance of the ischemic myocardium while increasing regional perfusion and diminishing lactate production after coronary arterial occlusion.[25]

Mechanisms of beneficial effects of nitroprusside in acute ischemic injury: Previous work in experimental animals with coronary occlusion in which direct epicardial electrodes were used to assess the extent of ischemic injury have supported the importance of maintaining mean arterial pressure, and hence coronary perfusion, to limit the ischemic area.[10] Whereas systemically administered nitroprusside decreases myocardial perfusion pressure, the reduction in total coronary blood flow observed with the agent may reflect a decrease in myocardial oxygen needs that predominates over the reduction of blood pressure.[24] Further, an increase in the reduced myocardial flow in ischemic areas has been reported in patients at the time of coronary bypass surgery.[26] Our clinical investigation, as well as other studies[11–17] in patients examining the actions of intravenously administered nitroglycerin, phentolamine and trimethaphan in acute myocardial infarction, has demonstrated that cardiac unloading accompanied by substantial reduction in systemic blood pressure reduced ischemic injury associated with acute anterior myocardial infarction. These studies have thereby suggested that overall reduction of myocardial oxygen consumption generally overrides the potentially deleterious effect of decreases in total coronary blood flow.

A potentially beneficial effect of cardiac unloading agents in improving reduced myocardial perfusion in coronary disease would appear to be the result of the considerable reduction in intraventricular diastolic pressure produced by nitroprusside. Consequently, the reduced intramyocardial pressure provides a transmural pressure gradient facilitating subendocardial blood flow despite reduced aortic pressure. On the other hand, a potentially adverse action of peripheral vasodilator agents in patients with coronary artery disease is the possible initiation of a coronary steal phenomenon through augmented flow to normal myocardium by way of nondiseased coronary arteries. In this regard, a recent experimental study[25] has shown that nitroprusside increased regional perfusion and decreased lactate production in ischemic myocardial regions after coronary occlusion, thereby suggesting enhanced collateral flow to the acutely ischemic zone rather than potentiation of the coronary steal mechanism.

Clinical implications: Our clinical findings are in agreement with the aforementioned experimental evidence that nitroprusside may exert a beneficial action in enhancing blood flow to ischemic heart muscle. Our observation that improvement in S-T segment mapping variables of ventricular ischemia was not closely correlated with the magnitude of reduction in indexes of myocardial oxygen consumption is consistent with this postulation. Our clinical data are consonant with the experimental work of da Luz et al.[25] in providing indirect evidence that nitroprusside may possess a separate action of augmenting regional blood flow to ischemic myocardium in patients with coronary artery disease, and thus it may improve myocardial energetics in this manner as well as by reducing myocardial oxygen needs by peripheral cardiac unloading mechanisms. An alternate consideration for the lack of correlation between changes in S-T segment elevation and indexes of myocardial oxygen consumption that requires further clarification is that S-T segment elevation as determined by precordial mapping may not be linearly related to the extent of ischemic injury. Moreover, a close relation between diminution of S-T segment elevation with infusion of nitroprusside and improved clinical course remains to be established.

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Computer Detection of Premature Ventricular Complexes: A Modified Approach

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The accuracy of a data reduction system for arrhythmia detection in identifying premature ventricular complexes was evaluated in continuous tape records of 30 patients in a coronary care unit. Computer analysis was performed with a Honeywell 316 digital computer. Threshold values for dominant complexes were automatically determined and recognition of premature ventricular complexes was based on differences in QRS configuration, timing and T wave configuration from the dominant complexes. Verification of the computer accuracy in detecting premature ventricular complexes was made with visual beat by beat inspection using a two channel strip chart recorder with simultaneous recording of the electrocardiogram and computer signal. This procedure allowed for exact beat to beat correlation and, thus, absolute determination of false positive and false negative identifications.

From 0.5 to 6 continuous hours of monitoring per patient (average 3.5 hours) were analyzed for a total of 105 monitoring hours. The basic cardiac rhythms noted were normal sinus rhythm, sinus arrhythmia, sinus tachycardia, demand pacemaker rhythm, atrial fibrillation and atrioventricular (A-V) dissociation with junctional rhythm. Premature ventricular complexes were evident in 28 tapes (93 percent) including 12 (43 percent) with multifocal premature ventricular complexes and 3 (11 percent) with ventricular tachycardia. The visual count of premature ventricular complexes totaled 7,921. Of these, 7,542 (95 percent) were properly classified by the computer. The total computer count was 8,717, representing a 13 percent false positive and 5 percent false negative identification rate. The false positive identifications of premature ventricular complexes occurred during periods of 10 seconds or more of continuous noise artifact and in the presence of atrial premature complexes conducted aberrantly. When these sections of tape were excluded, the computer had a less than 2 percent false negative and 3 percent false positive rate of identification of premature ventricular complexes.

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It is well documented that conventional coronary care unit monitoring techniques are unreliable in detecting arrhythmias of various types in patients with acute myocardial infarction.[1–4] As a consequence, false impressions are being generated of premonitory arrhythmias, the natural history of specific arrhythmias and results of drug therapy.[5] In response to an obvious need, there have been accelerated efforts to develop and validate computer systems for off-line analysis of continuous tape recordings as well as real time monitoring.[6–8] Accuracy of QRS detection in such systems has been demonstrated to be quite satisfactory under a variety of conditions.[4,6,9] Display of R-R intervals in histogram configuration and other plotting methods[4,7,9–13] have permitted recognition and quantitation of arrhythmia occurring at rest or during activity. Although these systems are not truly diagnostic, they provide for quantitative data reduction and therefore permit diagnosis of arrhythmias through verification with the actual electrocardiogram.[4]

The premature ventricular complex has been difficult to recognize consistently and with predictable accuracy using computer techniques.[6,14,15] The problems with various methods have been outlined in a recent conference report.[16] In this paper we describe in detail our experience with a modified computer system in detecting premature ventricular complexes. The tapes studied were randomly selected from a collection of routine coronary care unit monitoring tapes so that no special precautions were taken in collecting the data.

Material and Methods

Computer analysis is implemented on a Honeywell 316 digital computer. The storage contains 12,000 words, each with 16 bits. The computer system has a digital acquisition subsystem, direct multiplex control channels, an analog input system and high speed arithmetic unit options. The electrocardiogram is sampled at a rate of 60 samples/sec.

R wave detection and analysis: Threshold is determined automatically and QRS configuration is assessed on the basis of maximal negative secant in excess of the threshold value. Details of this technique have previously been described.[4] The QRS configuration is determined by the difference between the amplitude of the maximal negative slope (YNLOC) and the amplitude at the isoelectric point. This value is called YDEL. The isoelectric point is considered to be at sample points 10 to 18 preceding the maximal negative slope point. The average amplitude of the electrocardiographic signal at the isoelectric point for complexes of normal duration was determined for 100 consecutive complexes and called YISO. The amplitudes are averaged to avoid sensitivity to short periods of muscle noise artifact.

T wave configuration is determined in the following manner: The T wave point is calculated by moving forward 10 sample points from the point of maximal negative slope and includes 2 sample points preceding and following the 10th point, that is, 5 sample points. The average T wave amplitude for complexes of normal duration is determined from the five sample points for 100 consecutive complexes of normal duration. The difference between the average amplitude of the T wave and the average amplitude of the isoelectric point represents YT. The location YT was chosen early in the development of the T wave to avoid misclassification as a result of T wave distortion that may occur with premature atrial complexes. The locations of YISO, YDEL and YT are illustrated in Figure 1.

Assessment of QRS timing and prematurity is accomplished by first determining a dominant rhythm class. The most frequently occurring R-R interval (the mode) is found and, after searching in both directions, a minimal R-R interval frequency that is at least 5 percent below this mode value is defined. The range is called YRR. The classification "premature" or "prolonged" (compensatory time) is based on whether an R-R interval is shorter or longer than the dominant range for the R-R interval.

Since each patient tape is analyzed individually and the determination of "normal" is based on those complexes occurring most frequently, the mean value and standard deviation need to be determined for each variable, YISO, YDEL and YT. These determinations result in an overflow for a 16 bit integer. In addition, the use of floating point arithmetic requires computer time and core. Therefore, linear order statistical approximation to the standard deviation is used. YDEL is called abnormal when it is outside the limits of the mean value ± 4 σ. YT is called abnormal when it is outside the limits of the mean value ± 5 σ.

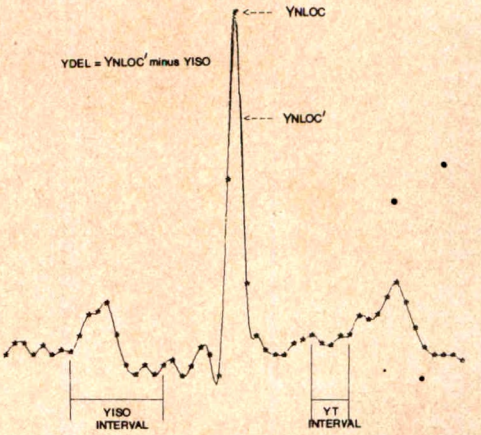


FIGURE 1. Location of YDEL, YISO and YT values taken from computer plot of sample points for one QRS complex. YNLOC is the maximal negative secant amplitude; YNLOC′ is the weighted maximal negative secant amplitude. See text for derivation of YISO and YT.

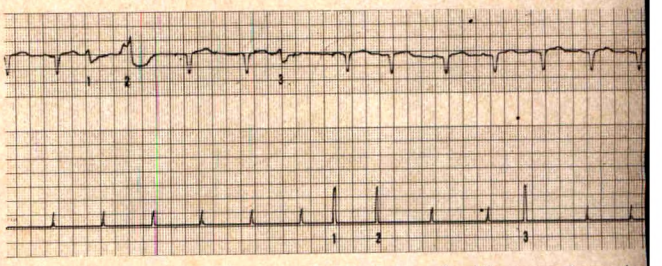


FIGURE 2. Electrocardiographic strip **(above)** with computer pulse output **(below)**. The height of the pulse is automatically doubled when a premature ventricular complex is identified (1, 2 and 3). The lag between the QRS complex and the pulse represents delay in the buffer system. The replay speed was four times real time; paper speed was 50 mm/sec.

Classification of QRS complexes: A decision table based on QRS configuration (YDEL), T wave configuration (YT) and timing (YRR) is used to classify four types of QRS complexes; (1) normal, (2) premature ventricular, (3) interpolated or late ventricular, and (4) atrial premature. A normal complex is that wave form with YDEL, YT and YRR within the range of the dominant rhythm. A premature ventricular complex is that wave form with YDEL and YT statistically different from the dominant QRS and with YRR premature. Interpolated or late premature ventricular complexes are those waveforms with abnormal YDEL and YT, but with YRR within the range of the dominant rhythm. Atrial premature complexes have normal YDEL and YT but are outside the range of YRR. All values for "normal" are automatically redetermined after every 100 complexes.

Monitoring tapes: All patients in a coronary care unit had magnetic tape recording (Hewlett-Packard model 3960) of a single lead electrocardiogram (lead II or V_1) for the entire period of their stay in the unit. Tapes analyzed in this study were selected at random from 30 such patients. The speed of the tape replay was four times real speed in order to permit simultaneous electrocardiographic write-out. When not validating, the replay speed is 16 times real speed.

```
TOD=  2055
  00000001111100000000
72          1
68          1
64          1
60          1
56          1
52          1
48          1
44          1
40          1
36          1
32          1
28          1
24          1
20          1
16          11
12          11
 8          11
 4          111
--------------------
    6     7     8     9
 68024680246802468024

   TOTAL BEATS:                      82
   TOTAL RANGE:                56- 94
   MODE RANGE:                 72- 76
   MAJOR MODE OCCURS AT:             74
   MAJOR MODE PERCENT:               72
  *NUMBER OF PREMATURE BEATS:         1
   PERCENT PREMATURE BEATS:           1
   RANGE OF PREMATURE BEATS:    62- 62
  *NUMBER OF COMPENSATORY BEATS:      1
   PERCENT COMPENSATORY BEATS:        1
   RANGE OF COMPENSATORY BEATS: 88- 88
```

FIGURE 3. Histogram for 1 minute of data with count and R-R interval measurements presented below. The histogram configuration, with slight widening of the base, suggests events other than normal sinus rhythm. The event is identified in the numerical data as one premature ventricular complex with a coupling interval of 620 msec and a compensatory time of 880 msec. The premature ventricular complex represented 1 percent of the data and thus was not shown in the histogram.

Verification of premature ventricular complex identification: Verification of computer accuracy in detecting complexes of ventricular origin was done by visual beat by beat inspection using a two channel strip chart recorder with simultaneous recording of the electrocardiogram and computer signal. The computer signal is a pulse, printed each time a QRS complex is recognized. The amplitude of the pulse is automatically doubled if the computer classifies the QRS as either a premature ventricular or interpolated ventricular complex (Fig. 2).

All data are put on digital tape for later print-out on a minute to minute basis in the form of a histogram. The R-R intervals, in milliseconds times 10, are plotted against frequency. In addition, the absolute numbers of R-R intervals for "premature" and "prolonged" (compensatory) beats are given. This procedure ensures that when the system is used clinically no data are lost if the frequency of premature beats is less than 3 percent of the data and thus not shown as a class in the histogram (Fig. 3).

Summary of system: The classification algorithm used in this study is based on a comparison of the frequency distributions for three variables: QRS configuration (YDEL), T

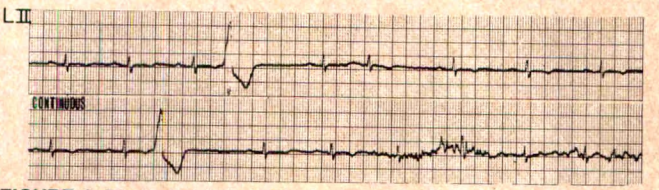


FIGURE 4. Rhythm strip (lead II) showing premature ventricular complexes, at least one atrial premature complex and an episode of baseline shift due to noise artifact.

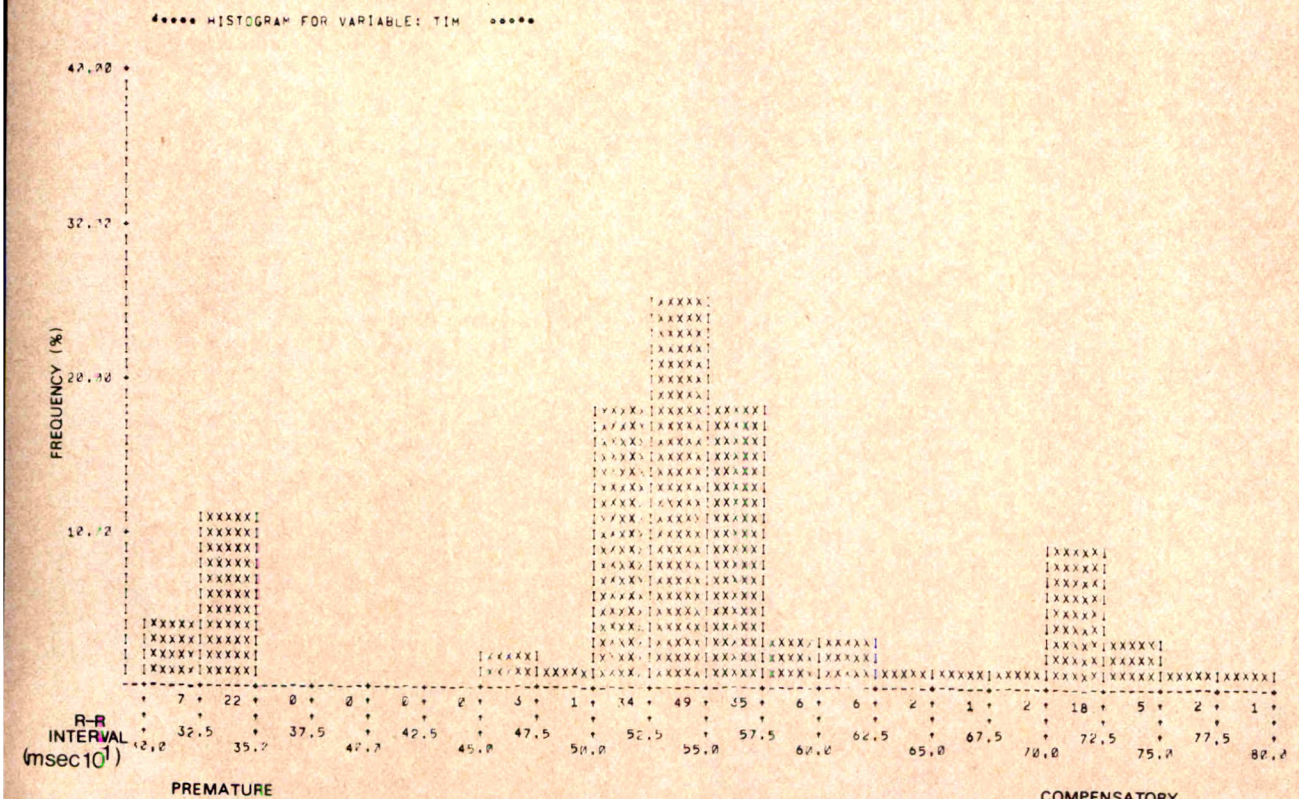


FIGURE 5. Percent of R-R intervals plotted against time for 200 consecutive complexes recorded from the patient whose rhythm strip is shown in figure 4. Three distinct clusters are seen. One cluster surrounds and another precedes the mode (premature). A third cluster occurs late, representing compensatory pauses.

wave configuration (YT) and timing (YRR). An electrocardiographic rhythm strip from a patient is shown in Figure 4. Examination of the R-R interval histogram (Fig. 5) of that strip reveals the presence of arrhythmia with both premature and compensatory periods. Figure 6 is a histogram for YISO. Examination of Figure 7 shows that there are distinct clusters of values for the amplitude difference YDEL. The relation of these clusters to the arrhythmia is evident in Figure 8, which shows the values for YDEL in relation to the duration of the R-R interval. One cluster is premature and has an abnormal YDEL value (labeled PVCs) and was verified to be premature ventricular complexes. Complexes having a normal value for

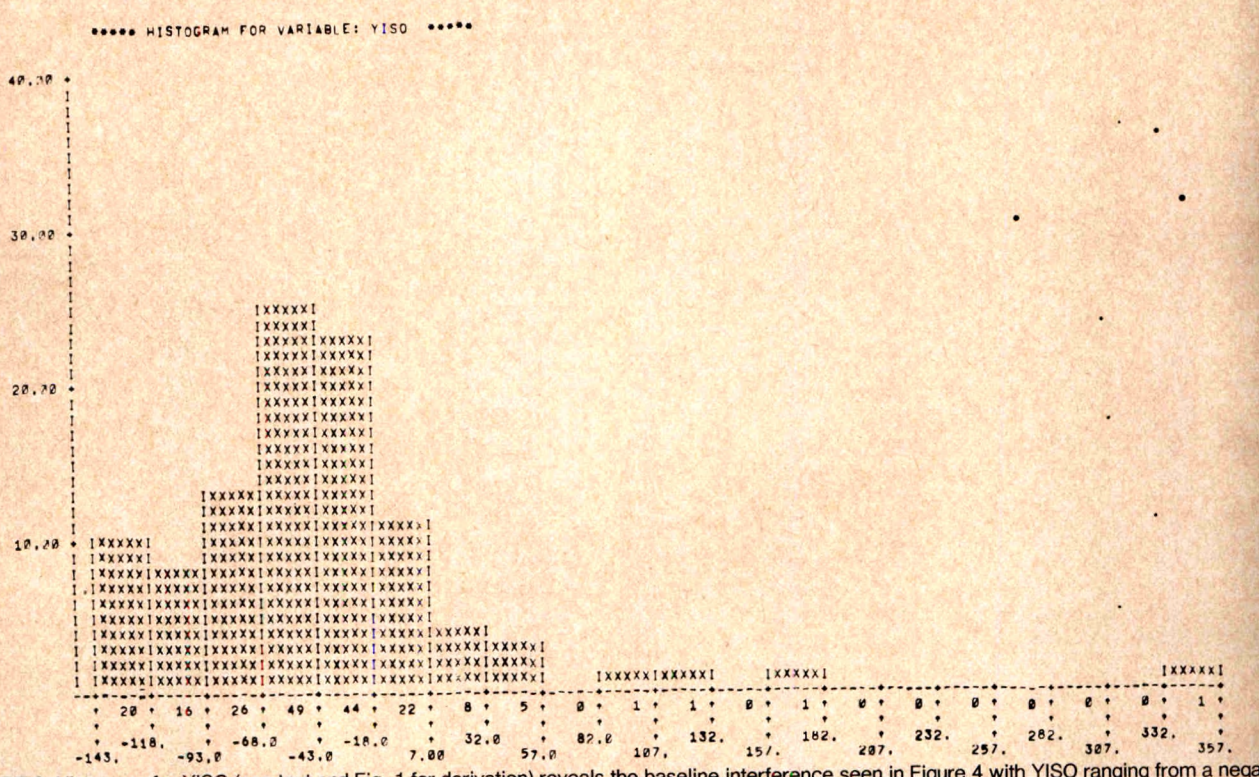


FIGURE 6. Histogram for YISO (see text and Fig. 1 for derivation) reveals the baseline interference seen in Figure 4 with YISO ranging from a negative 143 to a positive 357. Most complexes occur between −143 and +57.

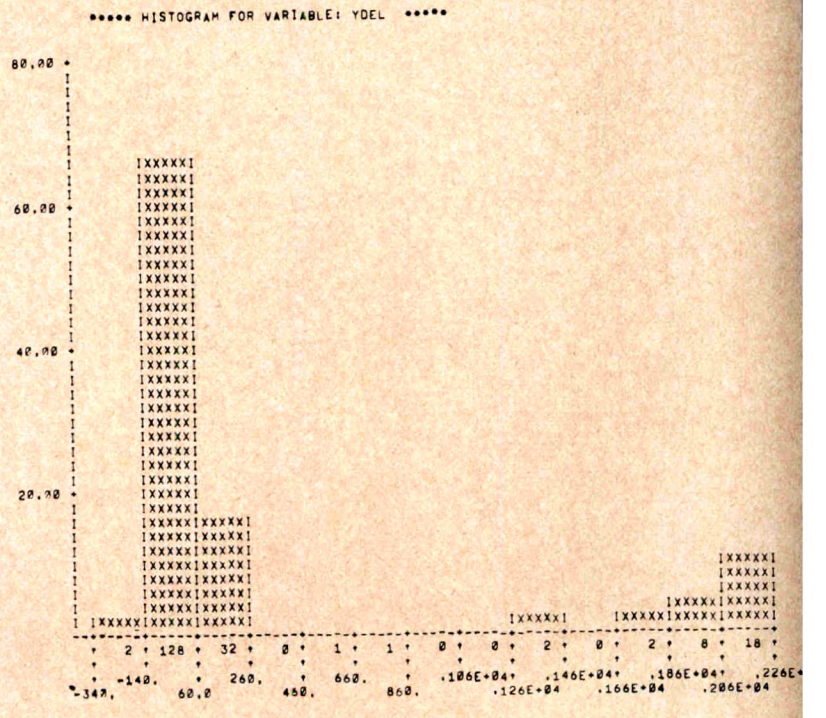


FIGURE 7. Three groups are seen when the percent of complexes is plotted against YDEL (see text and Fig. 1 for derivation). Those complexes with the greater YDEL value are premature ventricular complexes (see Fig. 8).

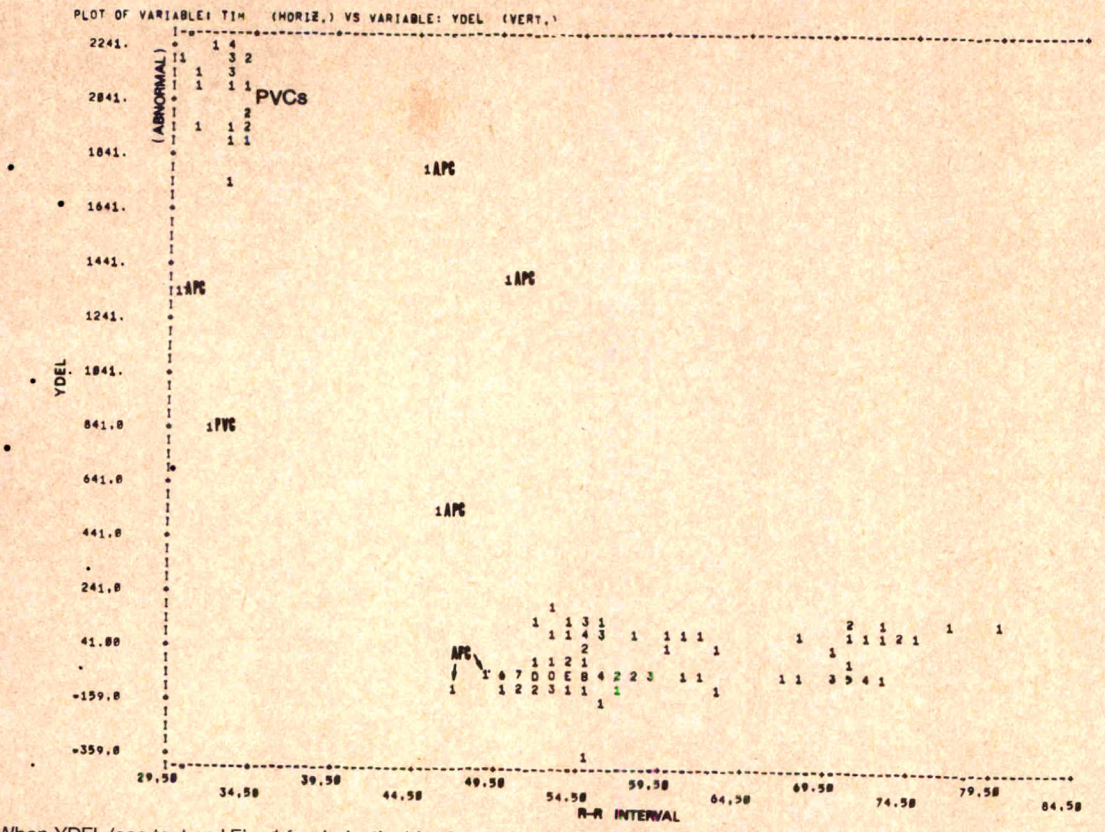


FIGURE 8. When YDEL (see text and Fig. 1 for derivation) is plotted against R-R intervals, those complexes with a YDEL value greater than 1,841 are premature ventricular complexes (PVCs) with the exception of one complex. The early complexes with a YDEL value of less than 1,841 are atrial premature complexes (marked APC).

YDEL (less than 1,841) are seen in the premature as well as dominant R-R range. This group of complexes which are premature but have a normal YDEL (QRS configuration) are premature atrial complexes. The distribution of YT (T wave configuration) is shown in Figure 9. Again, there are two clusters of data. Relating YT to the R-R interval (Fig. 10) reveals, as in the case of YDEL, that the premature complexes fall into two groups, those with a high negative YT value and those with a normal YT value. The premature ventricular complexes are identified as those outside the normal limits for YT. In the presence of interpolated ventricular complexes or marked sinus arrhythmia, the duration of the R-R interval of the premature ventricular complex may overlap the dominant rhythm classification. However, in these instances, the premature ventricular complexes are properly identified because the values for YDEL and YT are both abnormal.

Results

The 30 tapes analyzed contained a total of 105 monitoring hours representing 0.5 to 6 continuous monitoring hours per patient (mean 3.5 hours per patient). All 30 tapes had at least one episode of noise artifact, and 8 tapes (27 percent) were considered "noisy" (Fig. 1).

Basic rhythms: The basic cardiac rhythms were normal sinus (18 tapes; 60 percent); sinus arrhythmia (5 tapes; 17 percent); sinus tachycardia (4 tapes; 13 percent); atrial fibrillation (1 tape; 3 percent); atrio-

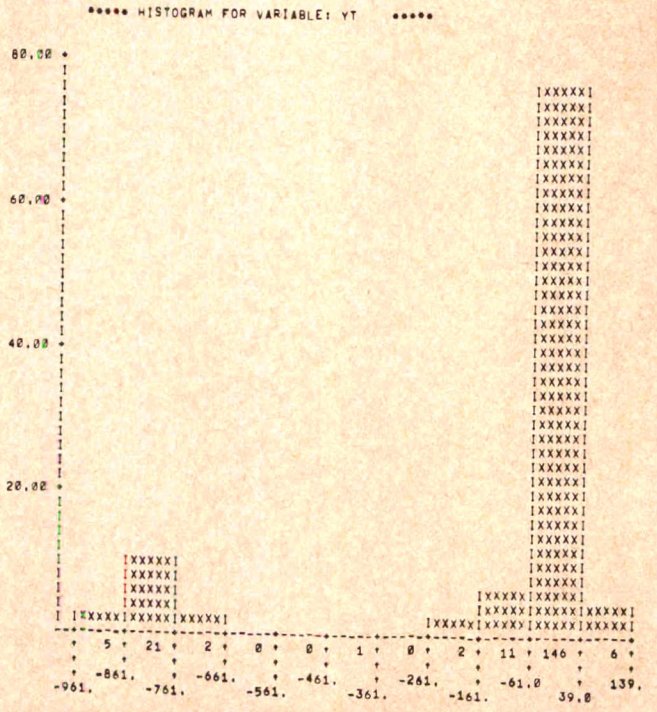


FIGURE 9. YT (see text and Fig. 1 for derivation) as plotted against frequency again shows two distinct groups of complexes with YT ranging from −961 to +139.

ventricular (A-V) dissociation with intermittent first degree and second degree heart block (1 tape; 3 percent); and demand pacemaker rhythm (1 tape; 3 percent).

Arrhythmias: Premature ventricular complexes or late ventricular complexes, or both, were evident in 28 tapes (93 percent) and were multifocal in 12 of the 28 (43 percent). Atrial premature complexes were evident in 10 tapes (33 percent). Other arrhythmias included junctional premature complexes (3 tapes; 10 percent) ventricular tachycardia (3 tapes; 10 percent); nonparoxysmal junctional tachycardia (3 tapes; 10 percent) fusion beats (2 tapes; 7 percent); paroxysmal atrial tachycardia (1 tape; 3 percent); atrial premature complexes with aberrancy (1 tape; 3 percent).

Recognition of premature ventricular complexes: The total visual count of premature ventricular

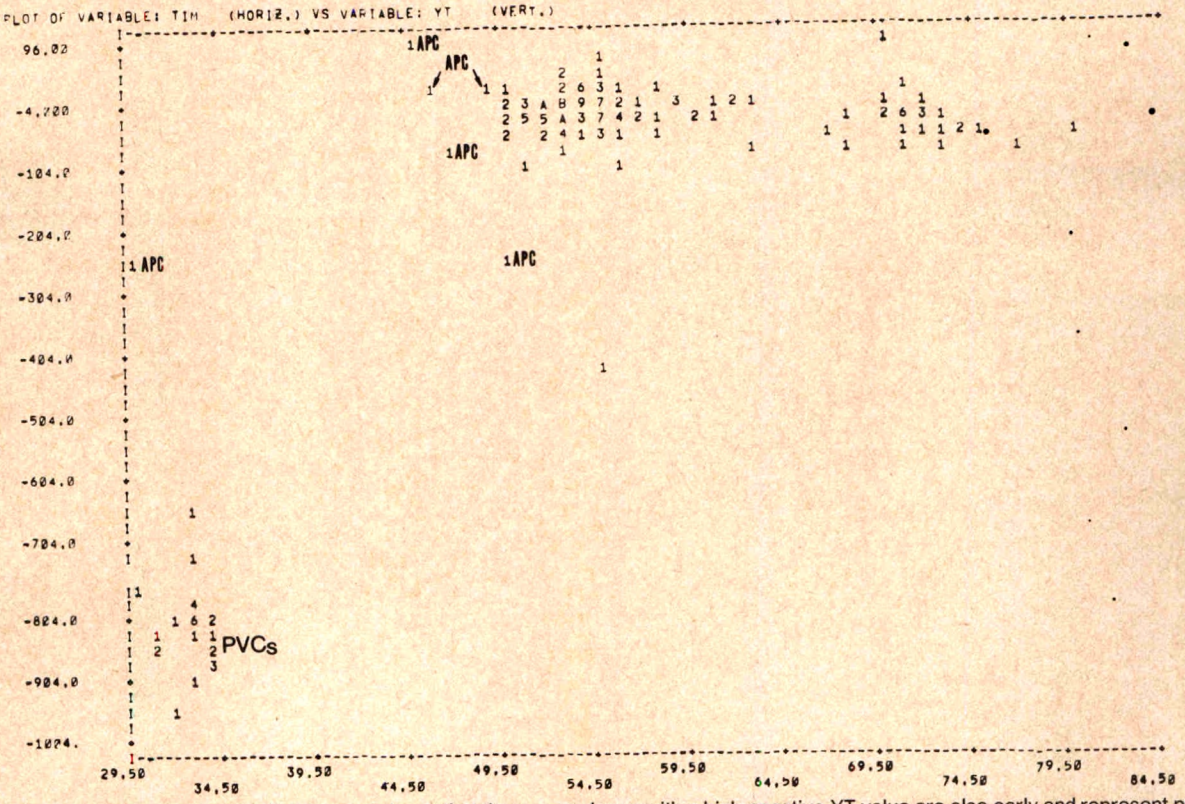


FIGURE 10. YT as plotted against the R-R interval shows that those complexes with a high negative YT value are also early and represent premature ventricular complexes (PVCs). Complexes that are early but have a low negative YT value are atrial premature complexes (APC).

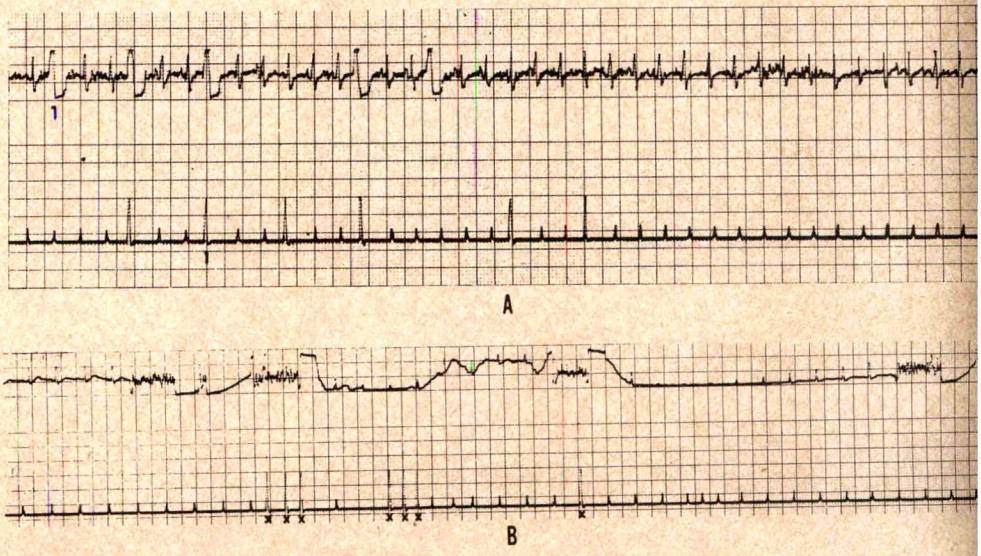


FIGURE 11. The computer correctly identifies premature ventricular complexes seen during one type of noise artifact **(A)** but makes a false positive identification during a different type of noise artifact **(B).** X = probably false positive premature ventricular complex pulse.

complexes was 7,921. The 28 patients with such complexes had an hourly count ranging from less than 1 to 322 (mean count 78/hour).

Of the 7,921 premature ventricular complexes, the computer properly identified 7,542 (95 percent). The total computer count of premature ventricular complexes was 8,717, representing a false negative identification of 379 complexes (5 percent) and a false positive classification of 1,175 (13 percent). The false positive classification occurred with the presence of continuous noise artifact of more than 10 seconds' duration and of the type seen in Figure 11B, and with atrial premature complexes with aberrancy. When only the sections of tape containing no more than 10 seconds of this type of continuous noise artifact are considered, the total number of premature ventricular complexes is 7,813. The computer correctly classified 7,682 (98 percent) of these and had a false negative and false positive identification rate of less than 2 and 3 percent, respectively.

The accuracy of the computer did not depend on the frequency of premature ventricular complexes in an individual patient. The computer properly classified a single premature ventricular complex occurring during 3 hours of monitoring in one patient and identified 1,281 of 1,284 complexes recorded during 6 hours of monitoring in another.

Discussion

Advantages of method: Although the system described here has not substantially improved the previously reported statistical accuracy for recognition of premature ventricular complexes,[6,7] it has certain advantages: (1) The situations in which inaccuracy of count are likely to be encountered are documented and predictable. (2) No intervention or preestablishment of criteria is required for identification of premature ventricular complexes. (3) Because the system updates itself every 100 complexes, changes in normal configuration with patient movement, intermittent bundle branch block, sinus arrhythmia and the wide variation in QRS configuration and timing concomitant with atrial fibrillation are less likely to result in false positive identification of premature ventricular complexes. (4) The plotting of actual QRS occurrence is readily available in histogram configuration, thus allowing for verification of computer accuracy. (5) Because the logic of the system is relatively uncomplex and the data points are relatively few, an audit technique can be used to check and refine the system. The parameters for contour analysis may be used as output to digital tape on a beat to beat basis. These numbers may then be reconstructed and examined in detail for each complex and for each computer classification. For example, if situations are found in which the system is obviously in error, each complex can be analyzed by the audit method. One does not have to wonder randomly about the reason for error or possible solutions.

The relative insensitivity of the system to occasional noise artifact resulting from patient movement or poor electrode contact results, perhaps, from the low sampling rate. Most artifact is of short duration and high frequency. Thus, sampling at 60 hertz will either miss the artifact or have a filtering effect on it, whereas a high sampling rate (200 to 1,000 hertz), will relay the artifact data to the analysis program, requiring the analysis algorithm to differentiate artifact from QRS complexes. Prolonged noise artifact does affect the system because it interferes with the determination of threshold value for the major class of complexes. If the computer cannot determine an average threshold, it cannot classify complexes. However, because updating occurs every 100 complexes, interference by noise artifact is corrected for and not perpetuated.

There is concern that increased accuracy in detecting premature ventricular complexes may require a two channel lead system, particularly in the analysis of exercise-induced arrhythmias.[17] This requirement would greatly increase the cost and complexity of computer monitoring systems, both on- and off-line. Although we cannot give definitive data at this time, preliminary evidence suggests that the system described herein may obviate the need for the two lead system. With our method, a degree of difference in QRS configuration that may not be appreciated by visual inspection of one lead (Fig. 12A, horizontal lead) is measurable and therefore readily identified by the computer (Fig. 12B). Further work is needed to document that within all premature ventricular complexes there is sufficient change in configuration in a single lead to permit recognition. If this were true, a second lead, while permitting visual identification of premature ventricular complexes, would not be necessary for computer classification.

Clinical application: Although the validation method utilized to determine the accuracy of detection of premature ventricular complexes has many shortcomings—for example, relatively few tapes were scanned (certainly not encompassing all possibilities of interference) and the validation was performed by

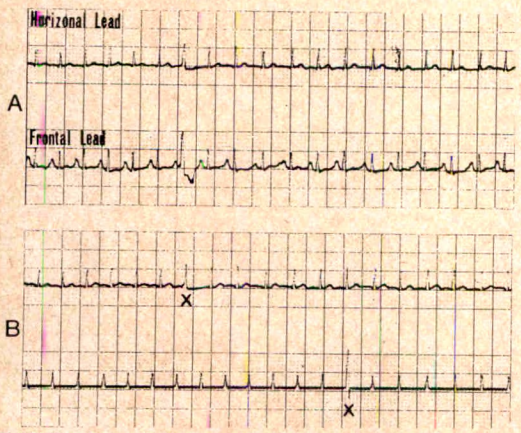


FIGURE 12. Rhythm strip from a simultaneous two lead recording. In the upper tracing of **A,** a complex is noted that may not be readily appreciated as a premature ventricular complex although it may definitely be identified in the frontal lead **(lower panel).** However, in **B** the changes in the QRS complex marked X are measurable and enable correct computer identification (the pulse marked X in the lower strip).

persons interested in the system—we have enough confidence in the system to apply it clinically. In addition to recognition of premature ventricular complexes and output in actual count per minute, episodes of ventricular tachycardia, heart block, atrial fibrillation, atrial tachycardia and junctional rhythm can easily be detected from the histogram configuration[4,7] and confirmed with the actual electrocardiogram. The histogram also permits identification of episodes of bigeminy and trigeminy because of the characteristic clustering of R-R intervals as a percent of the total complexes.[7]

The presence of multifocal premature ventricular complexes can be inferred from the coupling times of the ventricular complexes, multifocal complexes being less fixed in coupling periodicity. Also, if the configuration is sufficiently different, classes of ventricular complexes can be established. Refinements of the system, presently undergoing validation, provide for separate counts of coupled, interpolated and multifocal premature ventricular complexes. These measures will increase the clinical utility and reduce the post-computer processing time of the system.

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Significance of Pacemaker Recovery Time After the Mustard Operation for Transposition of the Great Arteries

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Pacemaker recovery time corrected for cycle length was measured in 24 patients 6 months to 3 years after the Mustard operation for transposition of the great arteries. This index of sinoatrial (S-A) nodal function was obtained by subtracting the control R-R interval from the first R-R interval recorded after 3 minutes of rapid atrial pacing at the superior vena caval-right atrial junction. Recovery times were compared with those of a control group of 54 children with various forms of congenital heart disease who had not had cardiac surgery and whose electrocardiogram revealed normal sinus rhythm.

The longest corrected pacemaker recovery time in the control group was 250 msec. Recovery time was normal (mean 115 msec) in 13 of the 24 patients who had undergone the Mustard procedure and prolonged (mean 472 msec) in the other 11. In 4 of these 11 a junctional escape complex was recorded before recovery of the S-A node.

The configuration of the P wave and the development of dysrhythmias in the postoperative follow-up period were compared in patients with a normal and a prolonged corrected pacemaker recovery time. The incidence of dysrhythmias was much smaller in the former group. Normal sinus rhythm after the first postoperative week was noted in 10 (76 percent) of patients with a normal corrected pacemaker recovery time but in only 2 (18 percent) of those with an abnormal recovery time. One patient with an abnormal recovery time died suddenly 26 months after operation in spite of good hemodynamic repair.

A prolonged pacemaker recovery time after the Mustard operation for transposition of the great arteries indicated that rhythm abnormalities were likely to develop, but a normal recovery time did not exclude abnormal sinus nodal function.

Disturbance of rhythm is a frequent and potentially lethal complication after the Mustard operation for transposition of the great arteries.[1–4] Late death as a result of dysrhythmia has been reported in several patients who had good hemodynamic repair.[3–6] Our clinical and pathologic studies[4,7] have shown that the main cause of dysrhythmias after the Mustard operation is injury to the sinoatrial (S-A) node and its arterial supply. Preliminary electrophysiologic studies in our laboratory[8] revealed no abnormalities in conduction in the atria, atrioventricular (A-V) node or His-Purkinje system; the main abnormality was in S-A nodal function. The pacemaker recovery time corrected for cycle length was significantly prolonged in four of nine patients studied. Our electrophysiologic methods for evaluating the specialized tissues after the Mustard operation were expanded after the original study and used in 15 additional patients. These additional studies confirmed that the internodal, A-V nodal and His-Purkinje pathways of conduction were intact and that the main defect was in S-A nodal function.

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In this study we correlated cardiac rhythm and P wave configuration with corrected pacemaker recovery time in 24 patients who had undergone the Mustard procedure. It was our aim to evaluate the validity of the corrected pacemaker recovery time in predicting which patients will be most likely to have progressive dysrhythmias after the Mustard operation.

Material and Methods

The response to rapid atrial pacing was compared in 24 patients with transposition of the great arteries who had undergone the Mustard operation and 54 control subjects considered to have normal sinus nodal function. The control subjects had congenital heart disease but had not undergone surgery. Their mean age was the same as that of the postoperative patients. Twenty-six were taking daily maintenance doses of digoxin, which were discontinued 24 hours before the study.

The postoperative patients were studied 6 months to 3 years after the Mustard procedure for transposition of the great arteries. Their ages ranged from 18 months to 22 years. Each was receiving maintenance doses of digoxin before the study.

All patients and control subjects were sedated with meperidine (0.5 mg/kg), chlorpromazine (0.25 mg/kg) and promethazine (0.25 mg/kg) 30 minutes before the study. In each subject one or more electrode catheters were inserted percutaneously into a femoral or brachial vein and manipulated under fluoroscopy to the superior vena caval-new right atrial junction. Atrial pacing was begun at twice threshold and the rate gradually increased to twice the resting sinus rate. Pacing was continued at this rate for 2 minutes and then suddenly stopped. Each patient underwent a total of two 3 minute periods of pacing at twice the sinus rate, and the mean value was reported. Before, during and after pacing three surface electrocardiographic leads were recorded at a paper speed of 100 or 200 mm/sec. In 10 postoperative patients His bundle electrograms and high and low atrial electrograms were recorded simultaneously. In the six most recent cases 10 different pacing rates were evaluated in addition to the rate twice the resting sinus rate.

The corrected pacemaker recovery time was calculated by subtracting the resting R-R interval from the immediate postpacing R-R interval. The R-R interval was used instead of the P-P interval because junctional pacemakers were sometimes the first to recover.

The corrected pacemaker recovery times of the control subjects were compared with those of the postoperative patients using Student's *t* test. The number of dysrhythmias per patient year in the postoperative patients with normal and abnormal recovery times were also compared using Student's *t* test.

Results

Control group: The mean corrected pacemaker recovery time in the 54 control subjects was 135 msec; the longest normal value was 250 msec.[11] The pacemaker to recover first after rapid atrial pacing was the S-A node in all of the control patients. An example of a normal corrected pacemaker recovery time is illustrated in Figure 1.

Postoperative patients: The corrected pacemaker recovery time was normal in 13 patients (range 0 to 225 msec; mean 115 msec). It was prolonged in 11 patients (range 255 to 1,200 msec; mean 472 msec) (Fig. 2). In 4 of the 11 patients with a prolonged recovery time a junctional escape complex was recorded before recovery of the S-A node after rapid atrial pacing.

In the six patients subjected to multiple pacing rates a biphasic effect of pacing was found. In the patients whose sinus rates ranged from 45 to 85/min pacing at twice the sinus rate produced a postpacing depression within 10 percent of the maximal depression found in the range of 10 rates.

TABLE I

Rhythm After First Postoperative Week in Relation to Corrected Pacemaker Recovery Time (CPRT)

	Normal CPRT	Abnormal CPRT*
Patients (no.)	13	11
Sinus rhythm only	10	2
Dysrhythmias		
Passive	3	9
Active	1	2
P wave height (mv)		
<0.05	1	3
0.05–0.1	3	4
>0.1	9	2

* More than 250 msec.

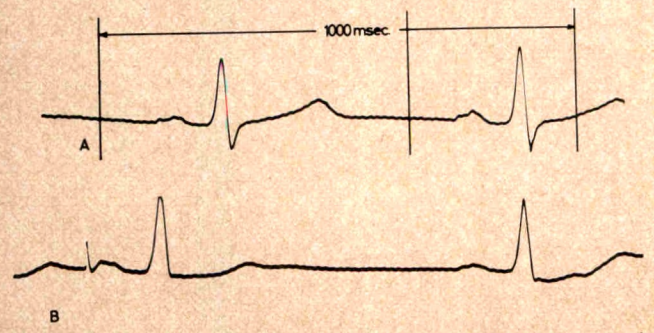


FIGURE 1. Normal corrected pacemaker recovery time in a control subject. The recovery time of 135 msec equals the R-R interval after atrial pacing **(B)** minus the resting R-R interval **(A)**.

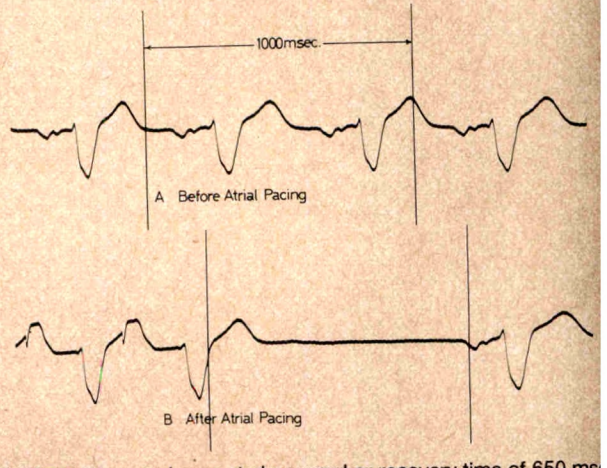


FIGURE 2. Abnormal corrected pacemaker recovery time of 650 ms in a patient after the Mustard procedure.

Correlation of pacemaker recovery times and dysrhythmias: Correlation of rhythms during the follow-up period with the corrected pacemaker recovery time (Table I) showed that only 3 of 13 patients (24 percent) with a normal recovery time had dysrhythmias during the follow-up period whereas 9 of the 11 patients (82 percent) with a prolonged recovery time had atrial dysrhythmias in this period. This difference was statistically significant. Figure 3 shows an example of normal sinus rhythm during the postoperative follow-up period in a patient with a normal corrected pacemaker recovery time. The surface electrocardiograms in Figures 4 and 5 were obtained during the follow-up study of two patients who had an abnormal corrected pacemaker recovery time; they show A-V dissociation by default and marked sinus bradycardia. The patient whose electrocardiogram is shown in Figure 4 died

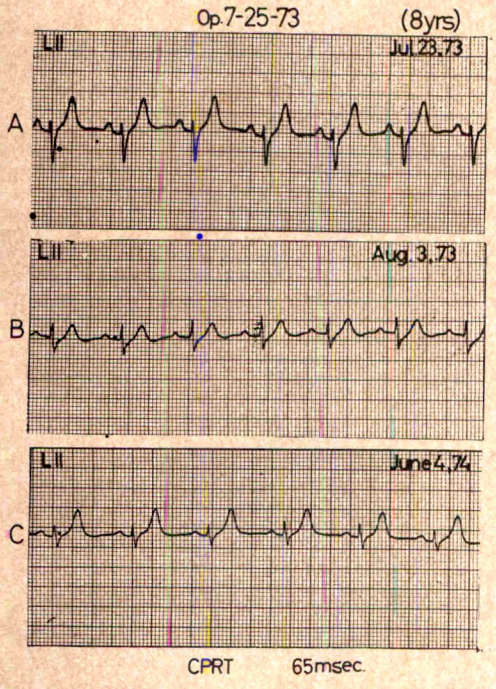


FIGURE 3. Three tracings from lead (L) II before **(A)**, 1 year **(B)**, and 2 years **(C)** after the Mustard operation in a patient who had a normal postoperative corrected pacemaker recovery time (CPRT) of 65 msec. Sinus rhythm is present in each panel.

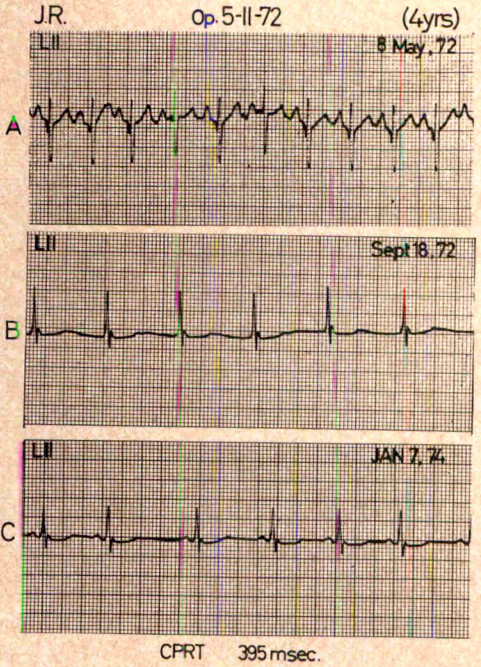


FIGURE 5. Three records from a patient with an abnormal corrected pacemaker recovery time of 395 msec showing normal rhythm preoperatively **(A)**, junctional rhythm **(B)** and sinus arrhythmia and low amplitude P waves **(C)**.

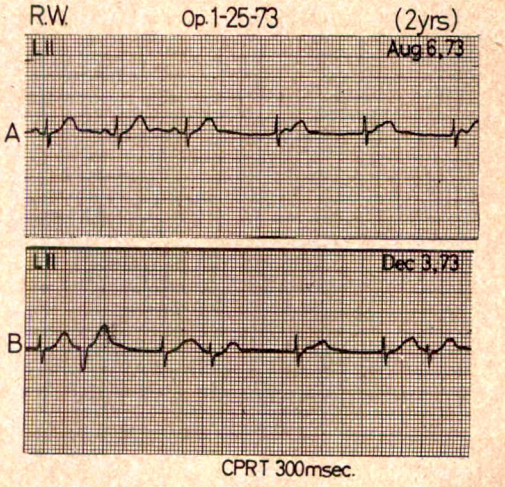


FIGURE 4. Lead II electrocardiogram 6 months **(A)** and 1 year **(B)** after the Mustard operation in a patient who had a prolonged corrected pacemaker recovery time of 300 msec. The tracings show A-V dissociation by default.

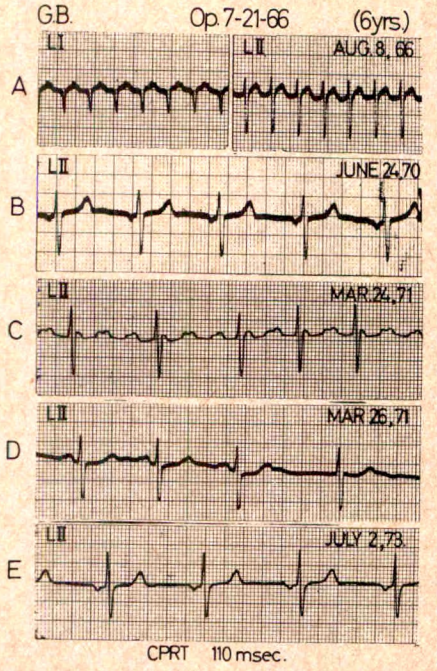


FIGURE 6. Follow-up electrocardiograms from a patient who had a normal corrected pacemaker recovery time of 110 msec but had several postoperative rhythm disturbances. **A,** supraventricular tachycardia and first degree A-V block; **B,** junctional rhythm; **C,** supraventricular tachycardia with variable block; **D,** A-V dissociation by default; **E,** junctional rhythm 7 years postoperatively.

suddenly 26 months after his operation in spite of a good hemodynamic result. By contrast, Figure 6 is from a patient who had several documented dysrhythmias during the follow-up period in spite of a normal corrected pacemaker recovery time. The P wave amplitude was significantly higher in the group of patients who had a normal corrected pacemaker recovery time.

Discussion

In adult patients with suspected sick sinus syndrome, the corrected sinus nodal recovery time is considered the most reliable index of S-A nodal function.[10–19] However, there are limitations to its usefulness.[19] Overdrive pacing at too rapid a rate may result in S-A nodal entrance block and a false negative result.[18] False negative results have also been reported without evidence of S-A nodal entrance block.[19]

Our study demonstrates a high degree of association between the corrected pacemaker recovery time and the abnormalities seen in the surface electrocardiogram during the postoperative follow-up period after the Mustard procedure. The incidence of sinus rhythm was significantly greater and the incidence of dysrhythmias smaller in children who had a normal recovery time. The corrected pacemaker recovery time was used to include subjects manifesting escape of a junctional pacemaker before recovery of the S-A node, but none of the four who recovered with junctional escape beat had a normal recovery time. The postpacing recovery by a junctiona pacemaker, rather than the S-A node, is additional ev idence of S-A nodal damage.

Previous studies[10,13,15] have shown that only one thir to one half of patients with the sick sinus syndrome hav an abnormal recovery time, thus suggesting that ab normal overdrive suppression of the S-A node does no occur in all patients. We do not know whether our pa tients who had normal sinus recovery had a normal S-A node. The electrocardiogram in Figure 6 is probabl from a patient with an abnormal S-A node in spite o normal pacemaker recovery time.

All of the postoperative patients and many of th control patients were taking digitalis up to 24 hour before study. In our previous study of children wit normal sinus nodal function we found no differenc between digitalized and nondigitalized patients.[11] I one study[20] in which patients were given short-ter doses of digitalis the sinus recovery time was shortene slightly. We therefore do not believe that digitali played a role in our findings.

We conclude that the corrected pacemaker recover time after the Mustard operation for transposition o the great arteries is a useful test. An abnormal recover time indicates that the patient is more likely to hav rhythm changes and a poor prognosis. However, a no mal corrected pacemaker recovery time does not ru out abnormal sinus nodal function.

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Variation in the Size and Distensibility of the Pulmonary Arteries in *d*-Transposition of the Great Arteries

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The relative size of the main pulmonary artery was determined from cineangiograms of 117 patients with *d*-transposition of the great arteries by calculating the ratio between the diameters of the main pulmonary artery and aorta. The pulmonary artery was largest in patients with ventricular septal defect or patent ductus arteriosus, or both, because of increased pulmonary arterial pressure and flow. In patients with an intact ventricular septum or with left ventricular outflow tract obstruction, or both, the main pulmonary artery was approximately the size of the aorta. Two cases of *d*-transposition and gross dilatation of the main pulmonary artery and hypoplastic first branch pulmonary arteries are presented. In these cases the ratio between the diameters of the main pulmonary artery and aorta was greater than in any of the other 117 cases studied.

Distensibility of the right pulmonary artery in 18 patients with *d*-transposition was assessed by determining the percent change in radius and the pressure-strain elastic modulus from the cineangiograms. In patients with intact ventricular septum the distensibility was similar to that reported for normal control subjects, but increased pulmonary arterial pressure due to a ventricular septal defect resulted in stiffer vessels. In comparison with these 18 patients the 2 patients with a grossly dilated main pulmonary artery had an excessively distensible main pulmonary arterial wall as indicated by a greater percent change in radius and abnormal tension-strain relation.

Excessive distensibility of the main pulmonary artery and hypoplasia of the first branch pulmonary arteries allowed a greater accommodation of left ventricular stroke volume in the main pulmonary artery and hence resulted in their gross dilatation.

The size of the main pulmonary artery in *d*-transposition of the great arteries is dependent upon its associated lesions. Although postmortem studies have shown that stenosis of the left ventricular outflow tract results in a main pulmonary artery that is smaller than the aorta, and that the presence of ventricular septal defect is associated with comparatively larger pulmonary arteries,[1] this information has not been quantitated. In subjects with normally related great vessels, gross dilatation of the pulmonary arteries of known and unknown origin[2] is well documented.

Anatomic abnormalities of the pulmonary valve apparatus[3,4] or of the vessel wall[5,6] are reported to result in aneurysmal dilatation. Hemodynamic factors such as increased intraluminal pressure[7] or turbulent blood flow as in atrial septal defect[8] and pulmonary valve stenosis[9] result in large pulmonary arteries.

This study reports on our measurement of the size of the main pulmonary artery from the angiograms of 117 patients with *d*-transposition of the great arteries and presents two cases of gross dilatation of the main pulmonary artery—a finding not previously reported in *d*-transposition. Distensibility studies were performed to clarify the mechanisms responsible for the variations in the size of the main pulmonary artery in *d*-transposition.

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Material and Methods

Pulmonary arterial size: To determine the variability of the size of the main pulmonary artery in *d*-transposition of the great arteries, we reviewed the cineangiograms of 117 patients less than 24 months of age studied at The Hospital for Sick Children, Toronto between 1967 and 1973. Twenty-four patients had an intact ventricular septum, 26 had associated patent ductus arteriosus and intact ventricular septum, 37 had a ventricular septal defect and 30 had left ventricular outflow tract stenosis. Patients with pulmonary arterial banding or systemic-pulmonary arterial shunts were excluded. The diameters of the main pulmonary artery and aorta were measured during systole in the lateral projection 2 to 3 mm above the sinuses. The result was expressed as a ratio. To validate the values obtained as a measure of pulmonary arterial size in patients with *d*-transposition the aortic diameter was measured in 18 patients, 8 with intact ventricular septum, 5 with a moderate to large ventricular septal defect with or without patent ductus arteriosus and 5 with moderate to severe stenosis of the left ventricular outflow tract. The result was expressed as a function of the body surface area. No significant difference in the diameter of the aorta was noted among the groups. Thus, it was concluded that in *d*-transposition the ratio between the diameters of the main pulmonary artery and aorta indicate the relative size of the main pulmonary artery among various groups.

Two patients with grossly dilated pulmonary artery: Two patients had a grossly dilated main pulmonary artery: Patient 1, with an intact ventricular septum and Patient 2, with a ventricular septal defect of moderate size (Table I). A mid-systolic murmur at the left sternal border and a high-pitched systolic murmur in both axillae and back was audible in both patients. The chest X-ray film in Case 2 showed evidence of hyperaeration of the left lung due to compression of the left main stem bronchus by the enlarged main pulmonary artery; this finding was confirmed on bronchoscopy and intraoperatively.

The cardiac catheterization data in these two cases are presented in Table I. Both patients had a small pressure gradient across the left ventricular outflow tract and between the main and the right pulmonary arteries. Patient 1 also had a small gradient between the main and left pulmonary arteries.

The angiographic findings in both patients were remarkably similar (Fig. 1). The main pulmonary artery was greatly dilated in both, and during peak systole measured 24 and 31 mm in diameter (corrected for X-ray magnification) in Patients 1 and 2, respectively. In both cases the left and right pulmonary arteries were small and the right pulmonary artery showed mild dilatation near its origin from the main pulmonary artery.

The Mustard operation was successfully performed in both patients, and the ventricular septal defect was closed in Patient 2. At operation, the right and left pulmonary arteries were found to be small and there was no definite localized stenosis of their ostia. Biopsy specimens obtained from the anterior wall of the main pulmonary artery in both patients were considered consistent with age. In Patient 2 a portion of the anterior wall of the main pulmonary artery was removed so as to relieve the compression of the left main stem bronchus.

Pulmonary arterial distensibility: The distensibility of the right pulmonary artery in 18 patients with *d*-transposition—10 patients with intact ventricular septum, 8 with associated ventricular septal defect—and in the 2 patients under special consideration, the distensibility of the main pulmonary artery was determined using an angiographic method[7,8]. Cineangiograms were recorded on 35 mm film at a rate of 60 frames/sec, and careful tracings of the pulmonary arteries were made during systole and diastole. Maximal and minimal diameters were measured midway between the origin and the first branch of the right pulmonary artery and of identical points at the maximal curvature of the main pulmonary artery in anteroposterior angiograms. The diameters were corrected for magnification using catheter image size.[10] The pulmonary arterial pressure was obtained using Statham transducer model P23-Db and was recorded before the cineangiograms. Percent change in radius and pressure strain elastic modulus were calculated according to the following formulas[7]:

$$\text{Percent change in radius} = \frac{\Delta R \times 100}{\bar{R}}$$

$$\text{Pressure strain elastic modulus (in g/cm}^2) = \frac{\Delta P \times \bar{R}}{\Delta R}$$

where ΔR = change in radius (difference between maximal and minimal values); $\bar{R}$ = mean pulmonary artery radius (average of maximal and minimal values); and ΔP = difference between systolic and diastolic pulmonary arterial pressures (that is, pulmonary arterial pulse pressure).

TABLE I

Cardiac Catheterization (C) and Intraoperative (I) Data in Two Patients With Dilatation of the Pulmonary Arteries

Case no.	Age (mo) & Sex	BSA (m^2)	Aortic O_2 Sat. (%)		Measurements: Pressures (mm Hg) LV	MPA	RPA	LPA	MPA/Ao Ratio	VSD	Diameter (cm) RPA	LPA	MP
1	9 M	0.31	47	C	46/6	33/9 (20)	10/6	NR	1.7	0	NR	0.6	2.4
				I	—	45/12	22/12	15/10	NR	0	0.7	0.8	NR
2	17 F	0.37	77	C	67/0–3	45/14 (27)	9/6 (PVW)	NR	2.4	65*	0.6	0.5	3.1
				I	—	43/27	NR	NR	NR	0.5 ×0.6	0.7	0.7	NR

*Ventricular septal defect measured as percent of aortic root.

Figures in parentheses indicate mean pressures.

Ao = aorta; BSA = body surface area (m^2); LPA = left pulmonary artery; LV = left ventricle; MPA = main pulmonary artery; NR = not recorded; PVW = pulmonary venous wedge; RPA = right pulmonary artery; VSD = ventricular septal defect.

Results

Size of main pulmonary artery: Table II summarizes the detailed angiographic analysis in 117 patients with *d*-transposition, and Table III shows the ratio between the diameters of the main pulmonary artery and aorta in these patients. In patients with an associated ventricular septal defect or a patent ductus arteriosus the main pulmonary artery was larger than the aorta and larger than that of patients with simple *d*-transposition, whose main pulmonary artery was slightly smaller than the aorta. When stenosis of the left ventricular outflow tract was present with or without ventricular septal defect, pulmonary arterial size was comparable with that of patients with simple *d*- transposition. The main pulmonary artery was smallest in patients with associated isolated stenosis of the pulmonary valve. In the two patients with a greatly dilated

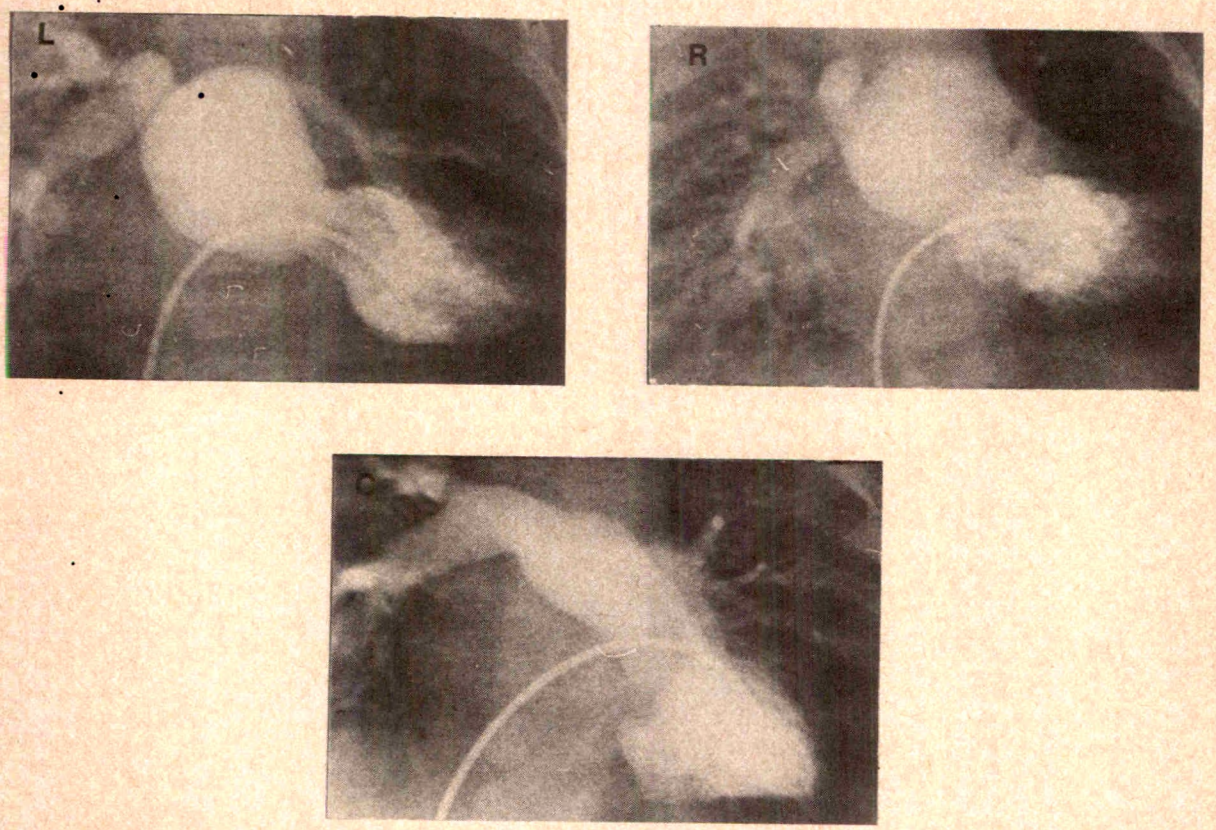


FIGURE 1. Left **(L)** and right **(R)** panels are the left ventricular cineangiograms showing gross dilatation of the main pulmonary artery and hypoplastic right and left pulmonary arteries in Patients 1(L) and 2(R). Note an apparently increased blood flow to the right lung in Patient 2, due to hyperaeration of the left lung. The central panel **(C)** is the left ventricular angiogram of a patient with *d*-transposition and a small ventricular septal defect and shows a more common relation between the size of the main and first branch pulmonary arteries.

TABLE II

Angiographic Data in 117 Patients With *d*-Transposition of the Great Arteries (*d*-TGA) (1967–1972)

		Persistent Ductus Arteriosus*				Ventricular Septal Defect As % of Aortic Root			Pulmonary Stenosis			
d-TGA	no.	Small	Moderate	Large	Total	<50%	>50%	Total	Valve	Subvalve	Subvalve + Valve	Total
Group I	24	...	...	...	...	...	...	...	...	...	...	...
Group II	26	5	10	11	26	...	...	...	...	...	...	...
Group III	37†	2	5	5	12	7 (41 ± 9)	12 (64 ± 15)	19	...	...	...	...
Group IV	30‡	0	5	0	5	23 (47 ± 9)	...	23	6	13	11	30

*Size assessed by degree of pulmonary arterial opacification and recirculation.
†Ventricular septal defect assessed by vision in 18 patients (small in 9 and moderate in 9).
‡Intact ventricular septum in 5 of 30, size of ventricular septal defect assessed by vision as moderate in 2 of 25.
Figures in parentheses indicate mean value ± 1 standard deviation.

main pulmonary artery the ratio between the diameters of the main pulmonary artery and the aorta was significantly greater than that of patients in their respective categories.

Pulmonary arterial distensibility: Table IV shows various measurements defining pulmonary arterial distensibility in the 18 patients with *d*-transposition and the 2 with a dilated main pulmonary artery. The patients with *d*-transposition and intact ventricular septum had a percent change in radius comparable with that reported for normal control subjects.[7] When account is taken of the patients' age[11,12] the corrected pressure-strain elastic modulus value is comparable with the reported values.[7] In patients with *d*-transposition and ventricular septal defect, the percent change in radius was not statistically different from that of the group with intact ventricular septum, but the pressure-strain elastic modulus value was higher.

Mean pulmonary arterial pressure in 18 patients with *d*-transposition was plotted against calculated pressure-strain elastic modulus values. A linear relation was noted; that is, the greater the pulmonary arterial pressure, the higher the pressure-strain elastic modulus

TABLE III

Ratio of Diameters of Main Pulmonary Artery and Aorta in 117 Patients With *d*-Transposition of the Great Arteries

	Ratio (±1 SD)	Patients (no.)
Group I (TGA)	0.97 ± 0.18	24
Group II (TGA + PDA)	1.13 ± 0.19*	26
Group III (TGA + VSD ± PDA)	1.18 ± 0.30†	37
Group IV (TGA + PS ± VSD ± PDA)	0.98 ± 0.31‡	30
A Pulmonary valve stenosis	0.80 ± 0.23	6
B Combined valve and subvalve stenosis	0.95 ± 0.32	11
C Subvalve stenosis	1.08 ± 0.41	13
Patient 1 (Group I) §	1.7	
Patient 2 (Group III) §	2.4	

*Statistically significant difference from values in Group I ($P < 0.005$).

†Statistically significant difference ($P < 0.005$) from values in Group I.

‡Difference not significant when compared with values in Group I but significant ($P < 0.01$) when compared with values in Group III.

§The patients with a grossly dilated main pulmonary artery.

PDA = patent ductus arteriosus; PS = pulmonary stenosis; SD = standard deviation; TGA = *d*-transposition of great arteries; VSD = ventricular septal defect.

TABLE IV

Distensibility Measurements in Patients With *d*-Transposition of the Great Arteries and the Two Patients With a Dilated Main Pulmonary Artery (mean ± 1 standard deviation)

	Age (mo)	BSA (m^2)	$\overline{PAP}$ (mm Hg)	PCR (%)	Ep (g/cm^2)	$\overline{R}$ (cm)
TGA with IVS	15 ±9	0.32	11.5 ±2.8	14 ±3	128 ±51	0.49 ±0.09
Patient 1	9	0.31	20	38.0	76	1.0*
TGA with VSD	14 ±10	0.42	38.5 ±14.7	15 ±3	345 ±103	0.48 ±0.07
Patient 2	17	0.37	27	36.0	104.0	1.3*

*Mean of systolic and diastolic main pulmonary arterial radius.

BSA = body surface area; Ep = pressure-strain elastic modulus; IVS = intact ventricular septum; PCR = percent change in radius; $\overline{R}$ = mean of systolic and diastolic radius of the right pulmonary artery in patients with *d*-transposition and of the main pulmonary artery in the two patients with a dilated main pulmonary artery; TGA = *d*-transposition of the great arteries; $\overline{PAP}$ = mean pulmonary arterial pressure; VSD = ventricular septal defect.

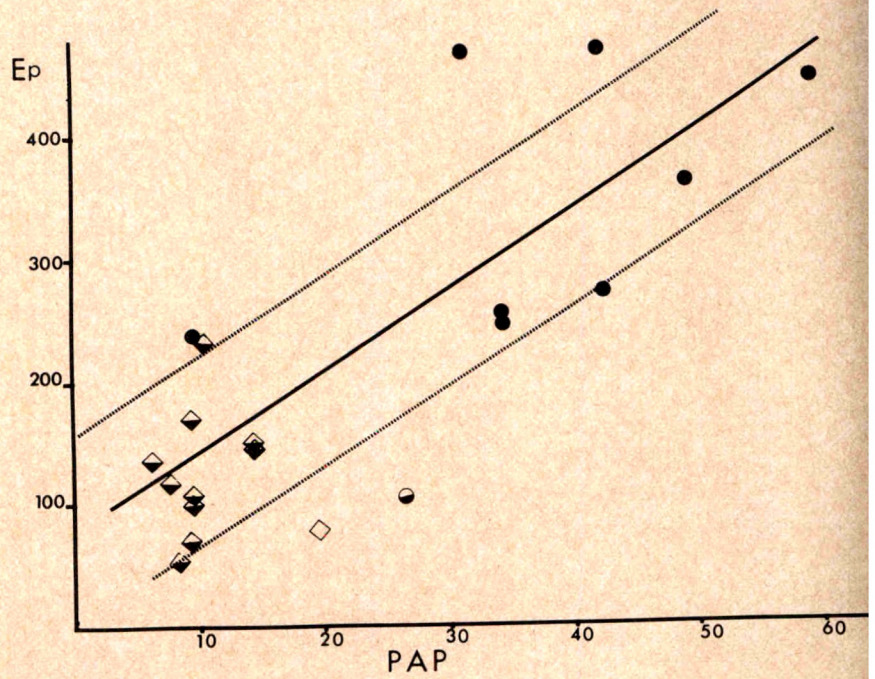


FIGURE 2. Mean pulmonary arterial pressure (PAP) in mm Hg and pressure-strain elastic modulus (Ep) (g/cm^2) show a linear relation in 18 patients with *d*-transposition. The **interrupted lines** show 1 standard deviation scatter. The patients with a ventricular septal defect **(closed circles)** have a high pressure-strain elastic modulus compared with those with intact ventricular septum **(semi-closed squares).** Both Patient 1 **(open square),** who had an intact ventricular septum, and Patient 2 **(semiclosed circle),** who had a ventricular septal defect, had decreased values for pressure-strain elastic modulus.

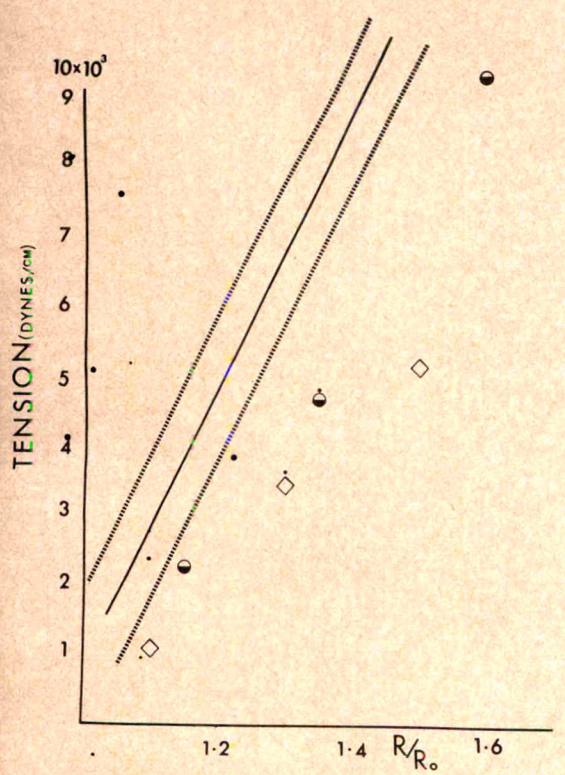


FIGURE 3. Tension-radius (R) diagram of the dilated main pulmonary arteries of the two patients. Radius is normalized by dividing by R_0, which is the calculated radius at zero tension.[8] **Solid** and **interrupted** lines are the mean and 1 standard error of the estimate of the values obtained from the normal pulmonary arteries.[8] For a certain radius the values for developed tension for both Patients 1 **(open squares)** and 2 **(semiclosed circles)** are lower than normal. Middle points **(dots over symbols)** are obtained by utilizing values for mean pressure and radius.

value (Fig. 2). In the two patients with a dilated main pulmonary artery the values for percent change in radius and the pressure-strain elastic modulus were lower in comparison with those of the 18 patients with *d*-transposition (Fig. 2).

Discussion

Our data show that patients with *d*-transposition and a ventricular septal defect or patent ductus arteriosus have a significantly larger main pulmonary artery than those with an intact ventricular septum. In the group with stenosis of the left ventricular outflow tract, the size of the main pulmonary artery was comparable with that of patients with an intact ventricular septum. Patients with *d*-transposition and ventricular septal defect or patent ductus arteriosus, or both, are reported to have increased pulmonary arterial pressure and flow,[13] and these factors seem to be responsible for the greater size of the main pulmonary artery.[7]

In our patients with *d*-transposition and a ventricular septal defect the value for pressure-strain elastic modulus was increased and was linearly related to the intraluminal pressure. The pressure-strain elastic modulus (Ep) for a nontethered circular elastic tube is related to the Young's elastic modulus (E) of the vessel wall material by the equation: $Ep = E(h/R)$, where h = vessel wall thickness, and R = radius of the vessel.[14] Thus an increase in the pressure-strain elastic modulus can be due to an increase not only in the Young's modulus of elasticity but also in the h/R ratio. It is reported that increased intraluminal pressure results in both increased vessel wall thickness and increased radius.[15] The three-fold increase in the pressure-strain elastic modulus in our patients suggests that both Young's elastic modulus (decreased elasticity) and h/R ratio played a role in this increase. In patients with *d*-transposition and intact ventricular septum and normal pulmonary arterial pressure, the normal pressure-strain elastic modulus indicated a normal vasculature.

Patients with grossly enlarged pulmonary artery: In the two patients with a grossly enlarged main pulmonary artery and normal or mildly increased pulmonary arterial pressure, the value for pressure-strain elastic modulus was decreased. Since a large increase in the radius was present in these two patients, the h/R ratio may well have been decreased so that the decrease in pressure-strain elastic modulus could have been due either to a decreased Young's elastic modulus or to a decrease in h/R ratio.

Roach and Boughner[16,17] have experimentally demonstrated that in poststenotic dilation the elasticity of the vessel material was decreased due to the effect of turbulence. Boughner and Roach[8] compared the tension-strain diagrams of the pulmonary arteries of the patients with poststenotic dilation and atrial septal defect who had normal pulmonary arterial pressures and found that, compared with normal values, the developed tension for a certain change in radius was lower in both. They concluded that the results indicated decreased elasticity of these dilated vessels. The tension-strain radius relation in both of our patients was similar to that reported for atrial septal defect[8] (Fig. 3). It seems likely that turbulence due to increased pulmonary blood flow caused increased distensibility in both patients. Bilateral hypoplasia of the first branch pulmonary arteries in both patients provided increased impedance to the forward flow from the main pulmonary artery, resulting in accommodation of the major part of the left ventricular output in the main pulmonary artery. Increased distensibility allowed for gross dilation of these vessels.

In conclusion, increased intraluminal pressure resulted in a larger and stiffer main pulmonary artery, and increased pulmonary blood flow with normal intraluminal pressure resulted in gross dilation of the main pulmonary artery through alteration of the vessel wall distensibility in our two patients. The latter mechanism may well determine the size of the main pulmonary artery in patients with *d*-transposition who have increased pulmonary blood flow without increased pressure.

Acknowledgment

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Echocardiographic Abnormalities in Acute Rheumatic Fever

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The echocardiographic velocity of circumferential fiber shortening and left atrial dimension were measured serially in two groups of children with acute rheumatic fever: Group I, six patients with valve regurgitation without congestive heart failure, and Group II, seven patients with regurgitation and congestive heart failure. In Group I, the initial velocity of circumferential fiber shortening was increased to 1.90 ± 0.31 circumferences per second (circ/sec) (mean ± standard deviation). In Group II, it was decreased (1.18 ± 0.25 circ/sec). In Group I velocity of circumferential fiber shortening subsequently decreased but remained above the normal level; in Group II it increased to exceed the expected normal value. Concurrent changes in left atrial dimension were observed in both groups. The initial left atrial dimension of Group I (2.2 ± 0.75 cm/m^2) was slightly increased and returned to normal (1.70 ± 0.32) on follow-up study. The left atrial dimension of Group II was greatly increased initially (2.70 ± 0.81 cm/m^2) and remained large (2.50 ± 0.67). Three patients in Group II experienced rebound during corticosteroid withdrawal. In each the velocity of circumferential fiber shortening decreased, suggesting impaired cardiac contractility. The echocardiogram thus facilitates serial assessment of the severity of carditis in acute rheumatic fever.

In the evaluation of acute rheumatic fever the severity of the carditis predicts the degree of residual chronic rheumatic disease. Responses of the erythrocyte sedimentation rate and other variables in the acute phase are used to determine both the presence and duration of rheumatic activity.[1] However, the elevation of the erythrocyte sedimentation rate is often as striking in patients with joint involvement as in those with severe carditis.[2]

In this study we evaluated the usefulness of the echocardiogram in assessing the severity of carditis throughout the course of illness in patients with acute rheumatic fever. Acute rheumatic fever is a pancarditis and the characteristic changes of pericarditis,[3] myocarditis[4] and valvulitis[5] may be demonstrated in the echocardiogram. This study reports the serial echocardiographic changes from the onset of disease through convalescence in two groups of patients with acute rheumatic fever, one with mild valve regurgitation and one with severe valve regurgitation and congestive heart failure.

Materials and Methods

The study group comprised 14 patients aged 8 to 17 years with acute rheumatic fever, representing all patients with this diagnosis at the University of Iowa Hospitals from July 1973 to June 1975. Periods of observation ranged from 5 to 19 months. Two patients had combined mitral and aortic regurgitation. In both patients the murmur of aortic regurgitation disappeared by the 5th hospital day. Four patients had pericardial effusion. One patient had chorea with no clinical manifestations of cardiac involvement.

Echocardiograms were performed using a Smith-Kline Ekoline 20 ultrasonoscope with a 2.2 or 5 megahertz unfocused transducer. The tracings were re-

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corded on a Honeywell 1856 strip chart recorder. All echocardiographic dimensions were measured from three sequential beats and averaged. The end-systolic dimension (LVDs) was measured just below the level of the mitral valve at the peak of the anterior movement of the left ventricular posterior endocardium (Fig. 1). The end-diastolic dimension (LVDd) was measured at the Q wave of the electrocardiogram. The mean velocity of circumferential fiber shortening (VCF) in circumferences per second (circ/sec) was calculated using the following formula[6]:

$$\text{VCF (circ/sec)} = \frac{\text{LVDd} - \text{LVDs}}{\text{LVDd} \times \text{LVET}}$$

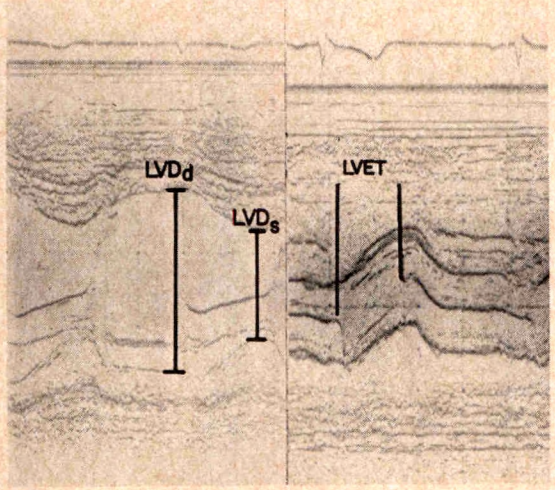


FIGURE 1. Composite echocardiogram. Left panel, the transducer is directed at the chordae tendineae, below the level of the mitral valve. The left ventricular diastolic dimension (LVD_d) is measured on the Q wave of the electrocardiogram. The systolic dimension (LVD_s) is recorded at the moment of peak anterior movement of the left ventricular posterior wall endocardium. Right panel, the transducer is directed to record the aortic valve leaflets. The left ventricular ejection time (LVET) is measured from the rapid opening of the aortic valve leaflet to closure.

The left ventricular ejection time (LVET)[7] was obtained from the aortic valve echocardiographic tracing. Left atrial dimensions were measured by the method of Hirata et al.[8] These dimensions were corrected for body surface area.

The 13 patients with cardiac involvement were classified into two groups: Group I, six patients with valve regurgitation but no clinical manifestations of congestive heart failure, and Group II, seven patients with valve regurgitation and congestive heart failure (Table I). Three echocardiographic studies were performed: (a) immediately on admission; (b) on the day that a course of corticosteroid therapy terminated or, if no corticosteroids were administered, on the 12th day after admission; and (c) during convalescence (the last time the patient was seen in the outpatient clinic). In three patients who experienced corticosteroid withdrawal rebound, defined as an abnormal increase in erythrocyte sedimentation rate, additional echocardiographic studies were performed: at the termination of steroid therapy, during rebound and on reinstitution of steroid therapy. Erythrocyte sedimentation rate was determined in all patients on the day echocardiographic measurements were performed.

Results

The patient with chorea who had no manifestations of carditis had normal echocardiographic findings, and his data are not included in the results. Of four patients with pericardial effusion, two manifested the effusion only in the echocardiogram; the other two had cardiac enlargement demonstrated by chest roentgenogram as well as echocardiographic evidence of pericardial effusion.

Mean velocity of circumferential fiber shortening (Table I): The normal pediatric values for the echocardiographic dimensions and mean velocity of circumferential fiber shortening have been established.[9] The mean velocity of circumferential fiber shortening on the day of admission (a) was greater in patients in Group I than in patients in Group II, whose value was lower than the normal value of 1.34 circ/sec[9] ($P < 0.001$). The mean velocity of circumferential fiber shortening in Group I decreased toward the normal value during

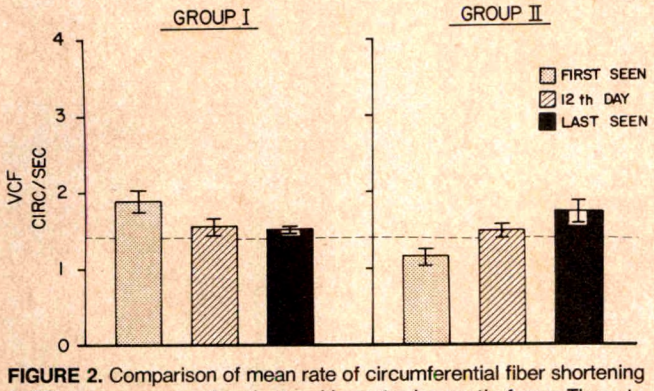


FIGURE 2. Comparison of mean rate of circumferential fiber shortening (VCF) in two groups of patients with acute rheumatic fever. The rate in patients with mitral regurgitation and no congestive heart failure (Group I) is increased initially and decreases to normal; that in patients with both mitral regurgitation and congestive heart failure (Group II) is initially decreased and increases to above normal. The horizontal line indicates the normal value for age.

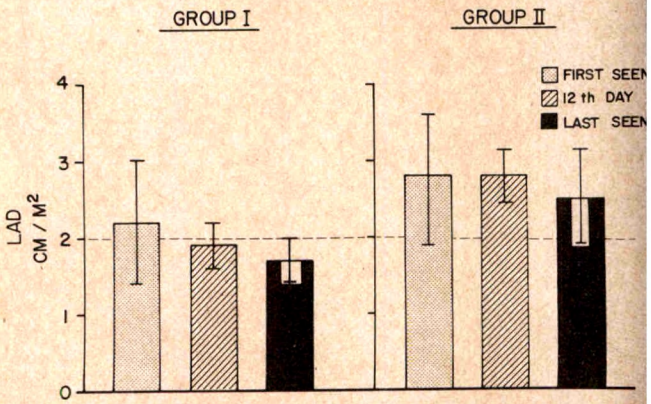


FIGURE 3. Comparison of left atrial diameter (LAD) in two groups of patients with acute rheumatic fever. The left atrial diameter is initially larger in patients with mitral regurgitation and congestive heart failure (Group II) but decreases in both groups. It remains larger than normal in Group II. The horizontal line indicates the normal left atrial diameter for age.

subsequent examinations and, on the last visit (c), was slightly greater than the expected value. This reduction was associated with a gradual disappearance of the murmurs of mitral regurgitation.

In contrast, the mean velocity of circumferential fiber shortening in Group II steadily increased, from initial values (a) that suggested depressed cardiac performance to elevated values on the last visit (c). Nevertheless, values differed significantly in the two groups only on day 1 and not on the two subsequent days (Fig. 2). Repeated measures analysis established that the trends within the two groups—decreasing mean velocity of circumferential fiber shortening in Group I and rising values in Group II—were different ($P < 0.05$).

Left atrial dimensions (Table I): Concurrent changes were observed in left atrial dimension (Fig. 3). The left atrial dimension was slightly increased in Group I during period a and returned to normal by pe-

TABLE I
Results in 13 Cases of Rheumatic Fever

Case no.	Age (yr)	Day	LVDd (cm)	LVDs (cm)	LVET (sec)	VCF (circ/sec)	LAD (cm/m²)	ESR (mm in 1 hr)
			A. Group I: Valve Regurgitation Only					
1	11	a	6.0	2.3	0.17	2.12	1.9	59
		b	4.4	2.7	0.18	1.50	1.8	15
		c	4.4	2.7	0.18	1.50	1.7	12
2	10	a	5.19	3.2	0.18	2.13	3.3	28
		b	5.59	4.3	0.18	1.28	3.3	25
		c	5.45	4.0	0.17	1.57	2.1	11
3	10	a	4.8	3.2	0.22	1.52	1.6	50
		b	5.0	3.4	0.23	1.39	1.5	29
		c	4.8	3.1	0.23	1.54	1.7	13
4	12	a	4.6	3.2	0.20	1.52	0.7	53
		b	4.5	3.2	0.18	1.60	1.9	25
		c	4.5	3.2	0.20	1.50	1.3	10
5	9	a	4.9	2.6	0.21	2.24	1.9	28
		b	4.8	2.7	0.22	1.90	1.7	5
		c	4.5	3.2	0.18	1.60	1.7	11
6	13	a	4.2	2.5	0.21	1.90	1.2	10
		b	4.4	2.6	0.22	1.82	1.2	20
		c	4.2	2.7	0.23	1.55	1.2	15
Mean ± SD			*3.3–4.7	1.7–2.8	0.19–0.27	1.34 ± 0.03†	2	<20
		a	4.94 ± 0.61	2.83 ± 0.41	0.19 ± 0.01	1.90 ± 0.31	2.2 ± 0.75	38.00 ± 18.94
		b	4.78 ± 0.46	3.15 ± 0.64	0.20 ± 0.02	1.58 ± 0.24	2.02 ± 0.67	19.83 ± 8.72
		c	4.64 ± 0.44	3.15 ± 0.47	0.19 ± 0.02	1.54 ± 0.03	1.70 ± 0.32	12.00 ± 1.78
			B. Group II: Valve Regurgitation Plus Congestive Heart Failure					
7	17	a	6.0	4.5	0.21	1.19	1.3	68
		b	4.4	3.2	0.21	1.30	1.3	30
		c	4.8	2.6	0.19	2.41	1.6	2
8	15	a	5.7	4.6	0.20	0.96	2.8	4
		b	5.0	3.4	0.18	1.78	2.8	21
		c	5.2	3.4	0.19	1.82	2.8	13
9	8	a	4.4	3.0	0.22	1.45	2.8	5
		b	5.1	3.25	0.21	1.74	3.7	34
		c	5.0	2.9	0.22	1.91	2.6	42
10	9	a	4.9	3.3	0.28	1.17	3.2	94
		b	4.6	3.1	0.26	1.25	3.2	18
		c	4.8	2.9	0.28	1.41	2.8	6
11	12	a	4.3	3.6	0.20	0.81	2.74	49
		b	4.8	3.2	0.19	1.75	2.40	6
		c	4.6	3.1	0.20	1.63	1.8	18
12	12	a	5.4	3.0	0.29	1.53	3.7	111
		b	5.2	2.9	0.32	1.38	3.9	16
		c	4.6	2.5	0.28	1.63	3.4	16
13	11	a	4.94	3.03	0.28	1.19	2.7	53
		b	5.0	2.90	0.30	1.40	2.5	24
		c	4.25	2.50	0.28	1.47	2.5	17
Mean ± SD			*3.3–4.7	1.7–2.8	0.19–0.27	1.34 ± 0.03†	2 cm/m²	<20
		a	5.09 ± 0.63	3.61 ± 0.67	0.24 ± 0.04	1.18 ± 0.25	2.70 ± 0.81	54.85 ± 40.75
		b	4.87 ± 0.28	3.13 ± 0.18	0.23 ± 0.05	1.51 ± 0.23	2.90 ± 0.91	21.28 ± 9.28
		c	4.75 ± 0.30	2.84 ± 0.33	0.23 ± 0.04	1.75 ± 0.33	2.50 ± 0.67	16.28 ± 12.81

* = Normal pediatric values.[9]
† = Mean ± standard error.
Day a = day patient first seen; Day b = 12th hospital day; Day c = last outpatient visit; ESR = erythrocyte sedimentation rate; LAD = left atrial dimension; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LVET = left ventricular ejection time; SD = standard deviation; VCF = mean velocity of circumferential fiber shortening.

riod c. During period a patients in Group II had greatly increased left atrial dimension that persisted through period c. The only significant difference between the two groups ($P < 0.01$) occurred during period c.

The end-systolic dimension was larger in Group II, the only significant difference occurring during period a ($P < 0.05$), reflecting the congestive heart failure present in this group. The measured end-diastolic dimension and left ventricular ejection time were also initially larger in Group II, but these differences were not significant. The mean erythrocyte sedimentation rate was increased initially in both groups and decreased toward normal by period b. In our series, the initial erythrocyte sedimentation rate had no predictive value.

Three patients experienced corticosteroid withdrawal rebound as evidenced by an increased erythrocyte sedimentation rate. One of these patients had an enlarged cardiac silhouette with pericardial effusion; the other two had no change in their cardiac manifestations. During steroid therapy the mean velocity of circumferential fiber shortening of this group was 1.52; during rebound, it decreased to 1.10 and with reinstitution of steroid therapy increased to 1.89. The erythrocyte sedimentation rate during rebound varied reciprocally with the mean velocity of circumferential fiber shortening (Fig. 4).

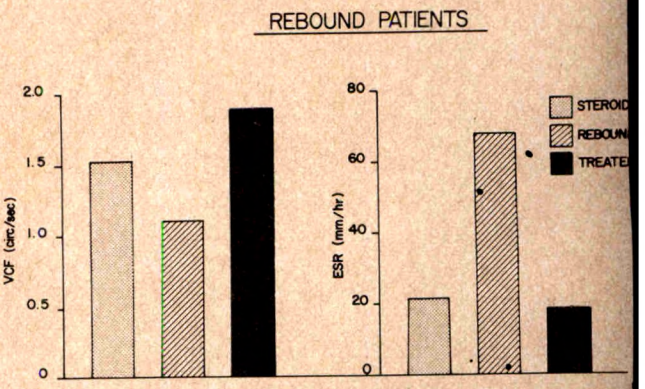


FIGURE 4. The mean rate of circumferential fiber shortening (VCF) and erythrocyte sedimentation rate (ESR) in three patients manifesting rebound after termination of steroid therapy. During rebound, the former rate is decreased and the latter increased; with reinstitution of steroid therapy, the former is increased and the latter decreased.

Discussion

The usual methods of evaluating patients with carditis of acute rheumatic fever are the identification and grading of significant murmurs, cardiac enlargement, the presence of pericardial friction rub and elevated levels of acute phase reactants. In patients with severe carditis congestive heart failure may develop in 5 to 10 percent of the first attacks.[10] Generally, these patients are left with severe residual heart disease.[11] Patients with mild carditis may have regurgitant murmurs that disappear with healing. Because the prognosis in patients with mild mitral or aortic regurgitation is so different from that in patients with severe regurgitation and heart failure, we tried to define objective measures of cardiac performance.

The cineangiographically determined mean rate of circumferential fiber shortening has been shown to provide an accurate measure of cardiac contractility.[6] Cooper et al.[12] found a high correlation between echocardiographic and angiocardiographic measurements of the mean velocity of circumferential fiber shortening, thus providing a noninvasive technique for accurately determining the cardiac inotropic state. The mean velocity of circumferential fiber shortening has been calculated in patients with mitral regurgitation using the left ventricular ejection time derived from the carotid pulse tracing.[6] Although the ventricle loses volume before aortic valve opening, the standard calculation of the mean velocity of circumferential fiber shortening is useful.

Mitral regurgitation: The echocardiogram distinguished between the hemodynamic effects of mitral regurgitation and those of the cardiomyopathy o rheumatic heart disease. Acute mitral regurgitation such as occurred in Group I produced increased mean ve locity of circumferential fiber shortening. With healing of valvulitis, the mean velocity returned to normal. This situation resembles that of acute experimental mitral regurgitation, which is known to reduce the impedance to left ventricular ejection, thereby allowing more complete ventricular emptying and increased velocity of myocardial fiber shortening.[13]

Congestive heart failure: Patients with mitral regurgitation and congestive heart failure initially had reduced mean velocity of circumferential fiber shortening. Despite the apparent advantages of decreased left ventricular impedance, cardiac performance was diminished. This finding strongly suggests that the dominant hemodynamic factor in this group was the acute rheumatic myocarditis. The mean velocity of circumferential fiber shortening increased in these patients during their hospital course and was supranormal in all on the last visit, thereby suggesting that the myocarditis was healing and the mitral valve regurgitation had persisted.

The prognosis of patients with congestive heart failure during active rheumatic fever is known to be worse than that of patients with mitral regurgitation alone. We suspect that the initial decrease in mean velocity of circumferential fiber shortening may be an important prognostic factor. Despite the later increase in the variable during convalescence, the long-term prognosis for patients with this finding may be poor. Patients with long-standing chronic severe mitral regurgitation experience a reduced mean velocity of circumferential fiber shortening and have a diminished inotropic state.[14]

Steroid withdrawal rebound: The decrease in mean velocity of circumferential fiber shortening in three patients during steroid withdrawal rebound suggests that their cardiac performance was transiently diminished. Another patient had an elevated erythrocy

sedimentation rate shortly before discharge. Despite this, there were no changes in the mean velocity of circumferential fiber shortening, a finding not consistent with rebound as seen in the three other patients. This diagnostic dilemma was solved when the rash of varicella appeared. Despite the rise in erythrocyte sedimentation rate, the persistent normal mean velocity of circumferential fiber shortening argued against the recurrence of rebound.

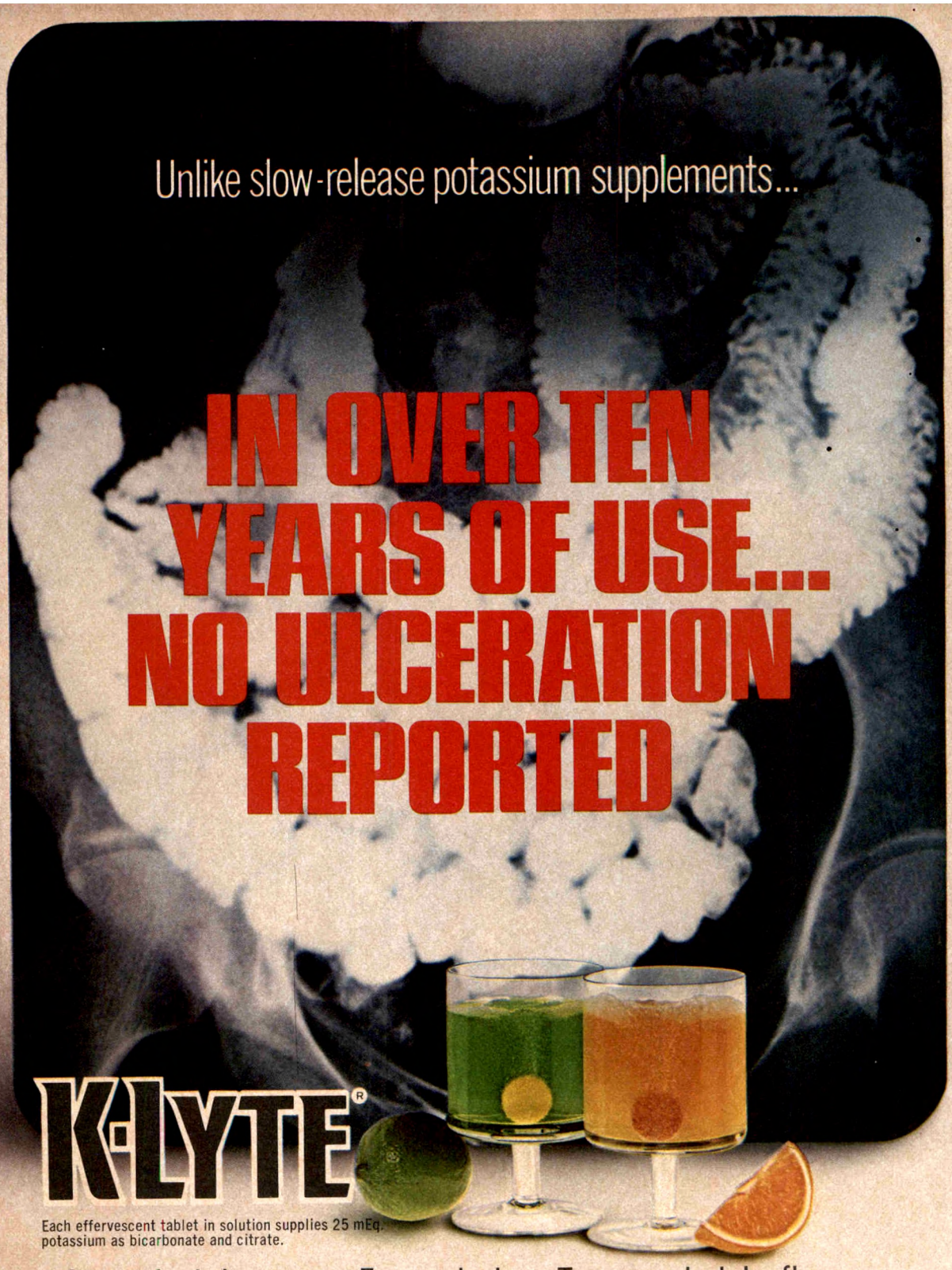
It is difficult to decide when the rheumatic process ends. The responses of variables such as erythrocyte sedimentation rate in the acute phase have been used for this purpose. However, these tests do not reflect the healing of carditis that can be assessed with echocardiographic measurement of cardiac performance.

Acknowledgment

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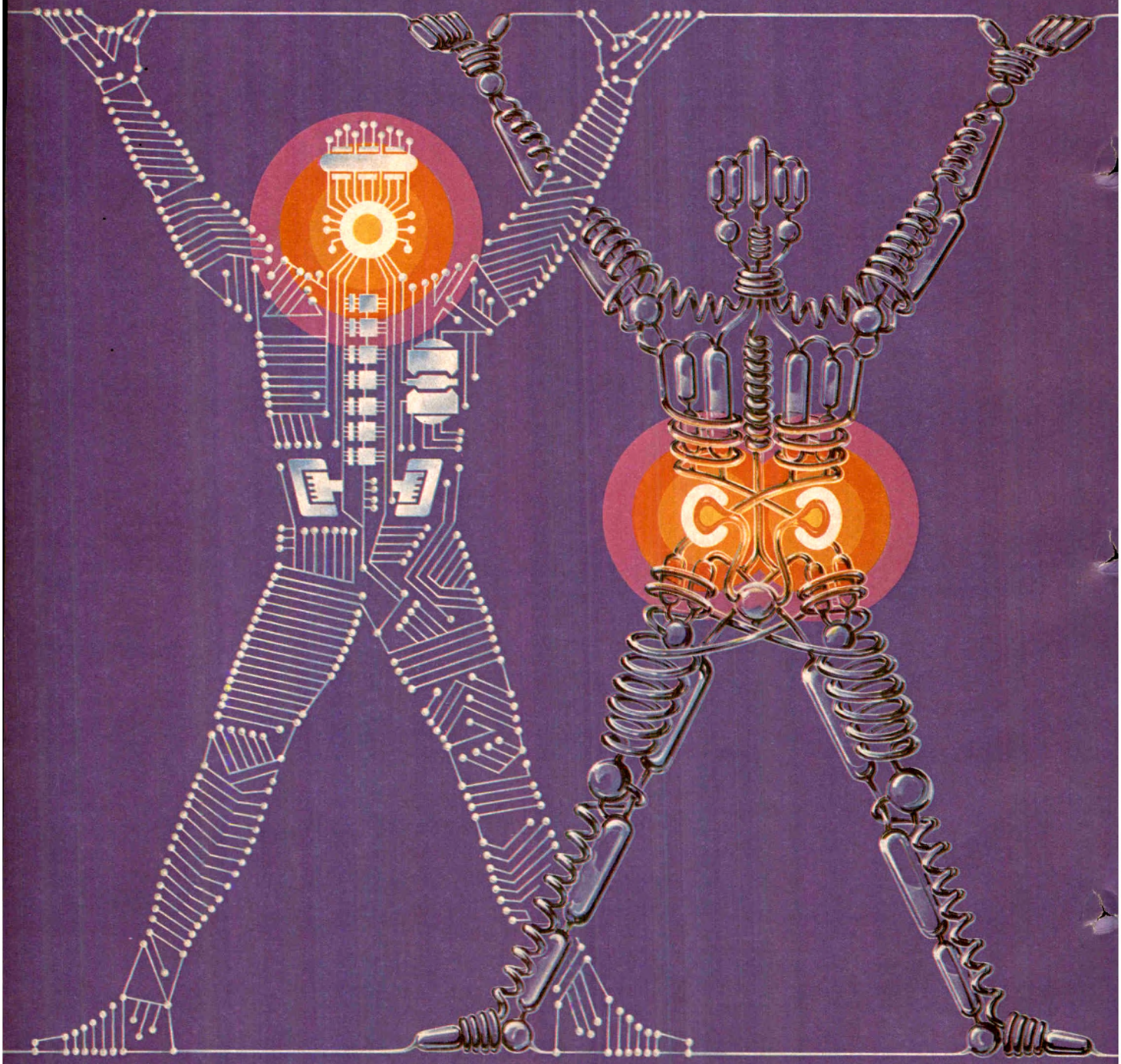
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Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

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Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria; thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

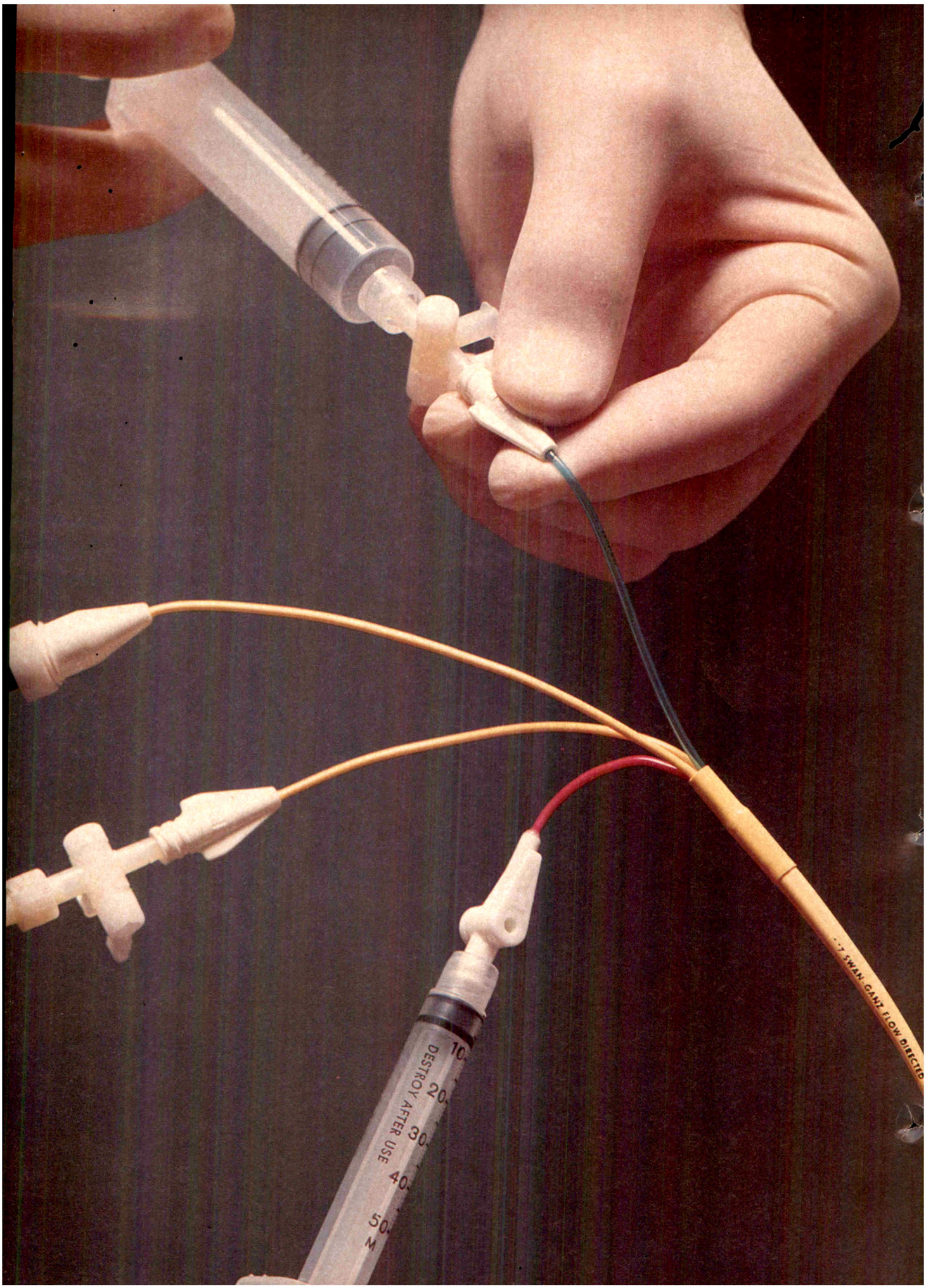
How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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Principles of oral anticoagulation

Practical Considerations

Identifying your patient at risk of thromboembolic complications

While every MI patient is not a candidate for oral anticoagulation therapy, a history of previous infarct or angina, persistent atrial fibrillation or congestive failure, severe hypotension or shock or serious arrhythmia may increase risk of thromboembolic complications.

In addition, certain procedures often place your surgical patient, particularly if he's over 40 years of age, in the high risk category—cup arthroplasty or pelvic surgery, heart valve replacement, reparative vascular surgery.

Your geriatric patient, too, is at high risk of thromboembolism if he's suffered a fracture—especially of the hip, pelvis or a lower extremity—or if his history includes venous insufficiency.

For any of these individuals, obesity, previous episodes of venous thrombosis or pulmonary embolism and a future including prolonged bed rest all increase the risk of thromboembolic complications, and make him a candidate for oral anticoagulation.

COUMADIN® is an Endo U.S. registered trademark.

Laboratory monitoring

For every patient receiving COUMADIN® (*crystalline* sodium warfarin), frequent laboratory monitoring is a key to effective therapy. Determine prothrombin time daily until results stabilize in the therapeutic range —1½ to 2½ times normal. Individualize dosage and administration as indicated by prothrombin time results. Determine subsequent prothrombin times periodically throughout the course of therapy.

Educating your patient

Because a patient is generally more reliable if he understands his condition and his medication, he should be made aware of the factors that may influence his prothrombin time and, therefore, his response to COUMADIN®—dietary change, travel, other medication, change in physical condition and abrupt environmental change. What's more, he should know the importance of regularly taking the exact dosage of COUMADIN® prescribed and of keeping every appointment with you and with the laboratory.

Therapeutic principles put into practice

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional and lumbar block anesthesia.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Pregnancy–COUMADIN® passes through the placental barrier, and the danger of hemorrhage to the fetus exists even to the point of fatal hemorrhage **in utero,** even in the accepted therapeutic range of maternal prothrombin level. Close observation and laboratory control are essential. The newborn may be particularly sensitive to sodium warfarin. There have been reports of birth malformations in children born to mothers who have been treated with warfarin during the first trimester of pregnancy. Whether warfarin was in fact the responsible agent has not been established. Therefore, women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed. If COUMADIN® must be used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks. **Lactation**–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Spinal puncture. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN®.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methylphenidate; monoamine oxidase inhibitors; nalidixic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates (in excess of 1 Gm/day); sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; ch hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (veget fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and s decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response ma unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion when their administration is started or stopped, the prothrombin time should be determined more than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutar and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of ference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activ prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent o bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition o anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding d anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR O DOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagn investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions ar extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulatio clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with min complications can best be achieved in cooperative and well-instructed patients, who keep the d informed of their status between visits. COUMADIN® patient aids are available to physicians on request

The administration and dosage of COUMADIN® must be individualized for each patient according t particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin reflects the depression of vitamin K-dependent factors, namely Factors VII, IX, X and II, the factors affe by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a able method. The blood prothrombin time should usually be determined daily after the administration o initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subseq prothrombin time determinations should be based upon the physician's judgment of the patient's relia and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable vals for prothrombin time determinations have usually fallen within the range of one to four weeks. factory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the no prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of do is provided by breaking scored tablets in half. The individual dose and interval should be gauged b patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general coagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and su procedures requires close liaison between attending physicians, surgeons and dentists. Interrupti anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maint at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants to, during, or immediately following dental or surgical procedures, it is recommended that the dosa COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the co level. The operative site should be sufficiently limited to permit the effective use of local procedures f mostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. U these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN® with Heparin–Since a delay intervenes between the administration of the initial dose an therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergen administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injec COUMADIN may be administered together in the same syringe. It should be noted that heparin may the prothrombin time; and therefore, when patients are receiving both heparin and COUMADIN®, the sample for prothrombin time determination should be drawn just prior to the next heparin dosage preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcuta injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readil trolled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or pare administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual ble melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprot binemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMA may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually corre problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombino states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic prothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imp numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 1

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intraven intramuscular use in a box of 6 units. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 1 thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Wa Injection. 75 mg: Unit consists of 1 vial, 75 mg; sodium chloride, 15 mg; thimerosal, 0.3 mg. adjusted with sodium hydroxide, accompanied by a 3 ml ampul Sterile Water for Injection.

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*Present as crystalline sodium warfarin isopropanol clathrate.

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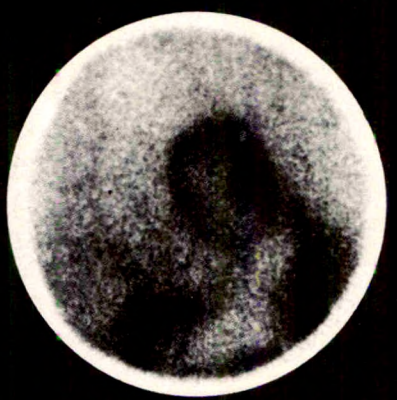
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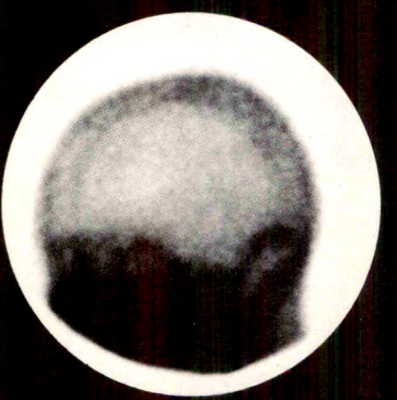
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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

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Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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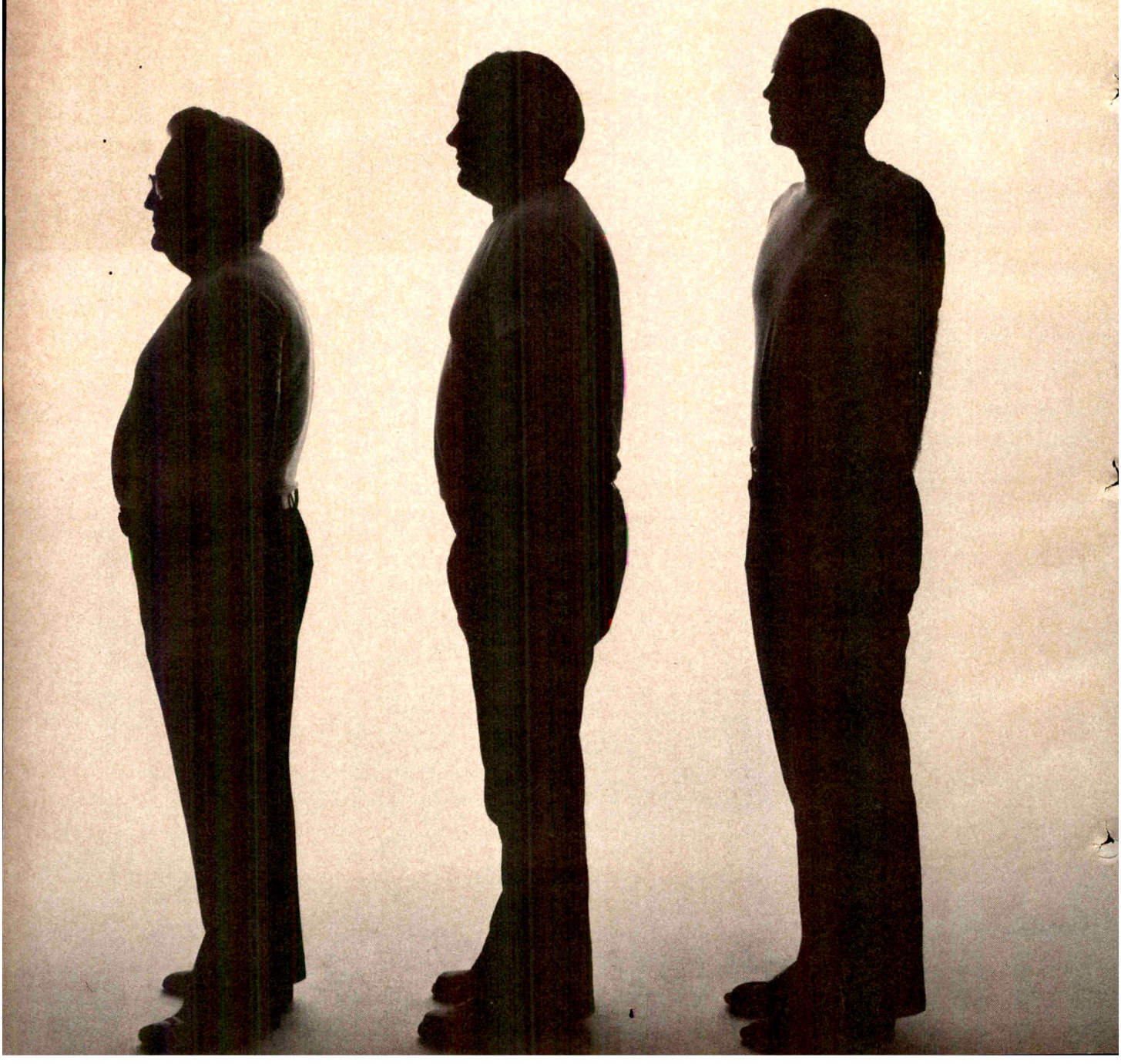
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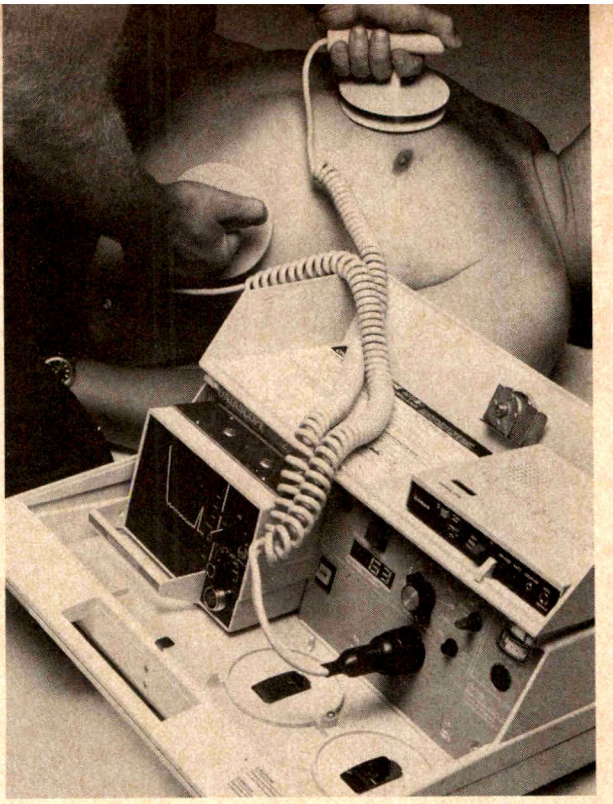
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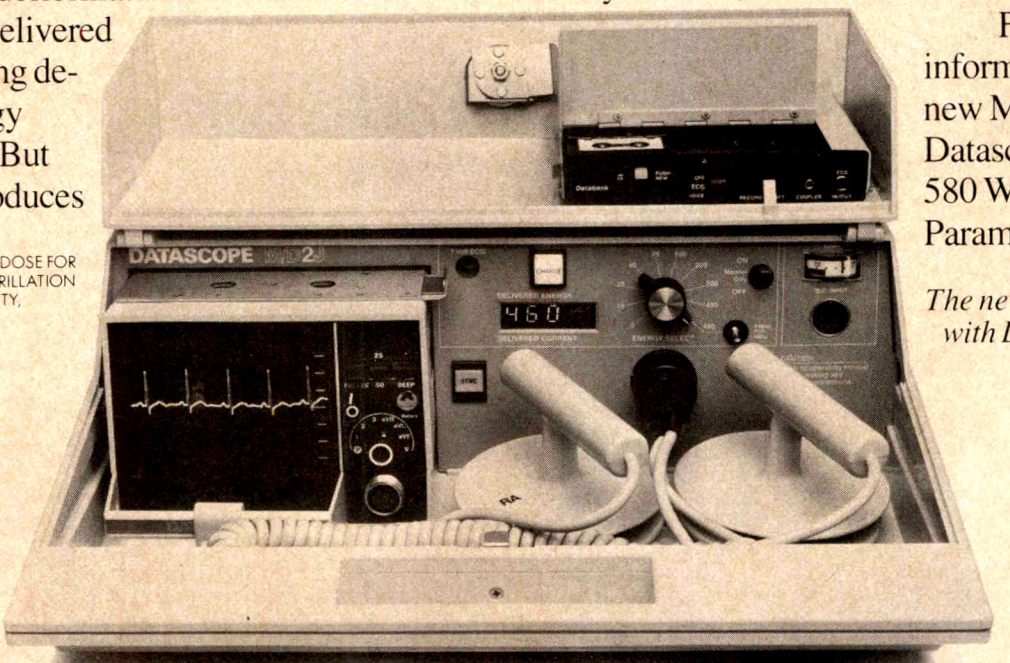
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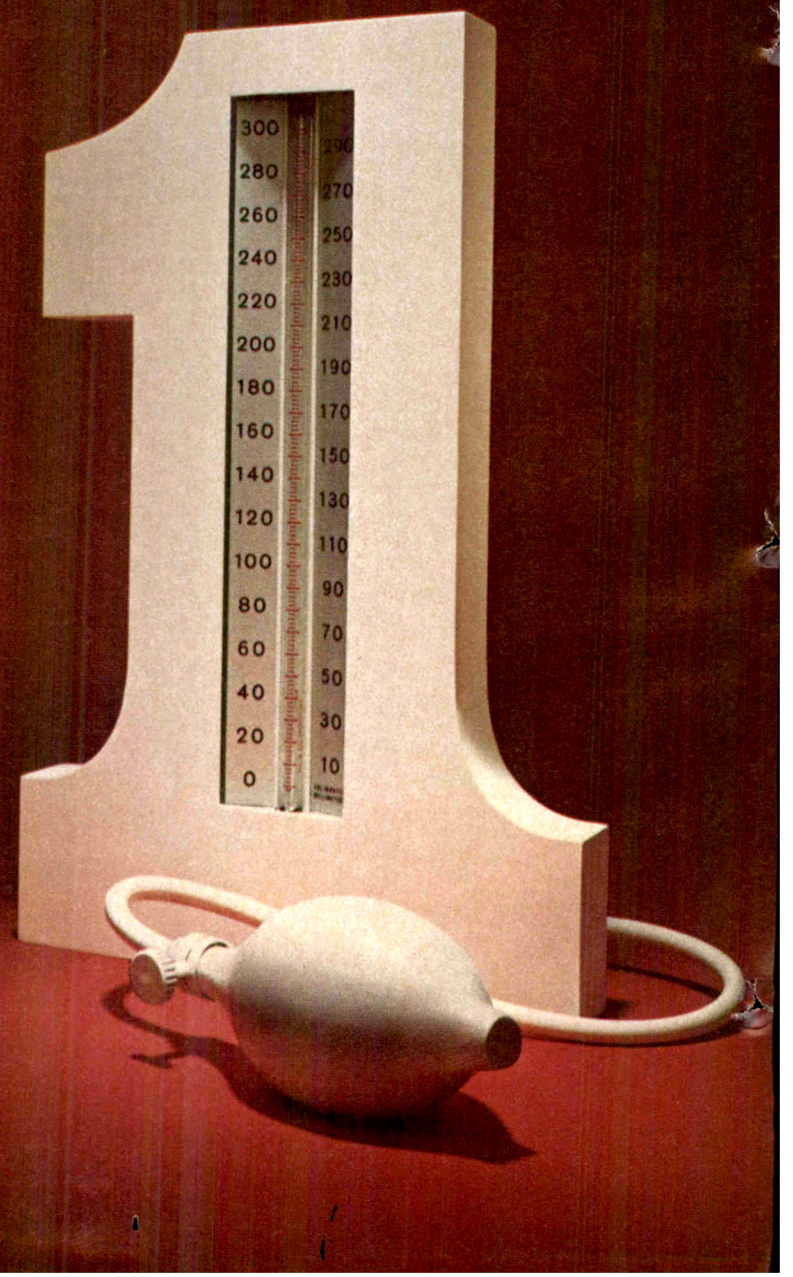
*TACKER, JR., W.A.: ELECTRICAL DOSE FOR DEFIBRILLATION. CARDIAC DEFIBRILLATION CONFERENCE, PURDUE UNIVERSITY, PGS. 121-7, OCT. '75.

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addendum

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In hypertension

HydroDIURIL®

(Hydrochlorothiazide | MSD)



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Use in Pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

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Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

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Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

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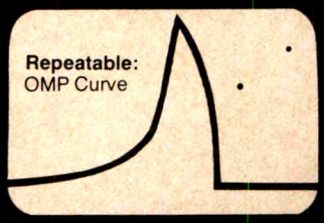
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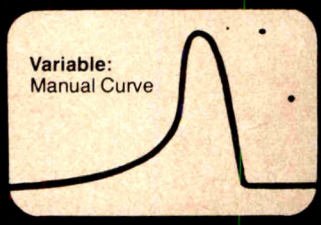
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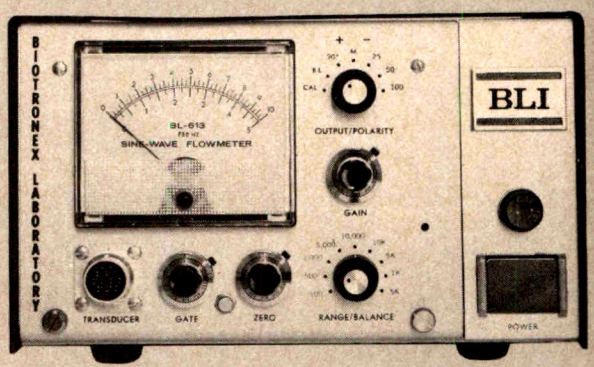
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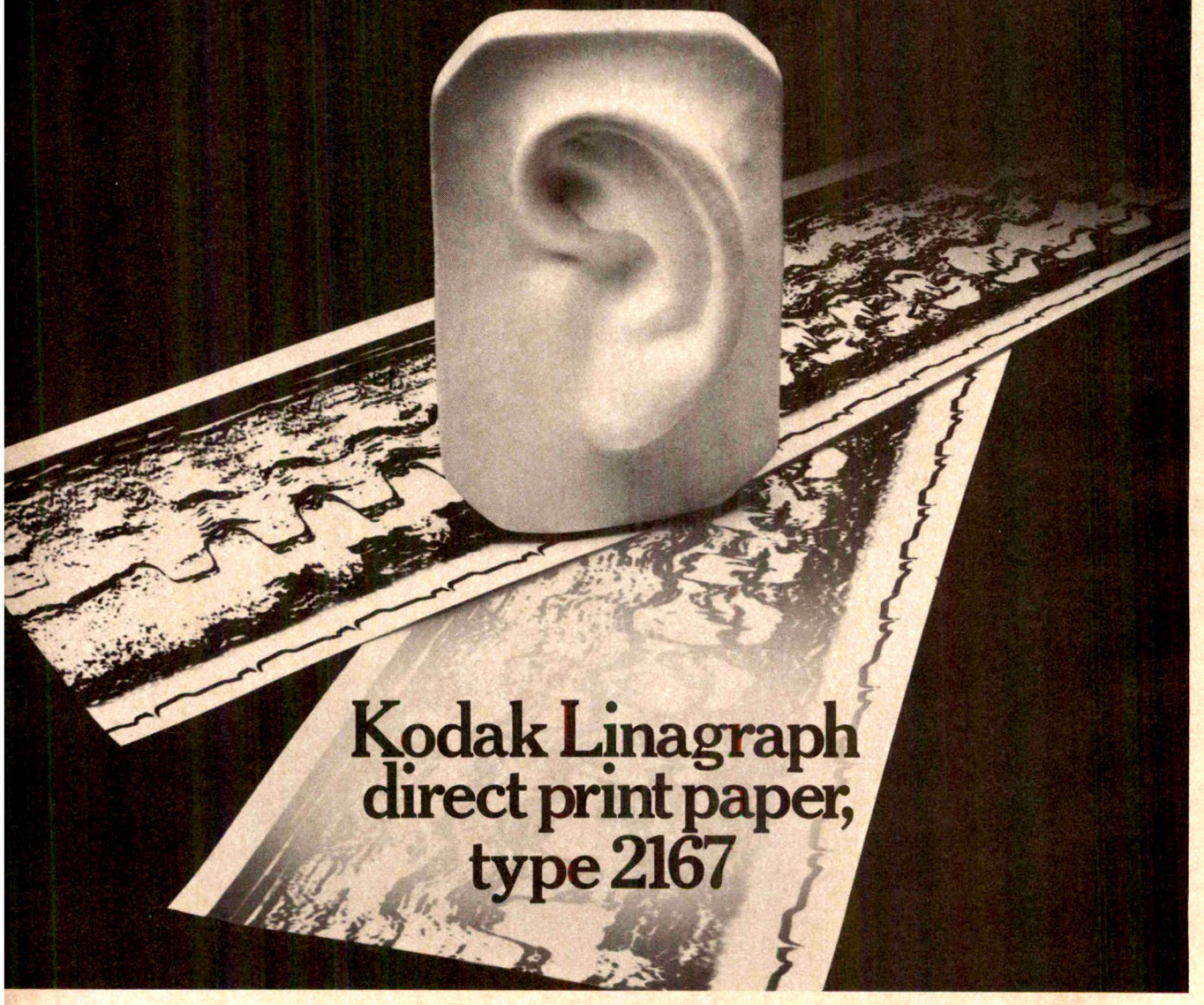
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Surgical Treatment of Degenerative Mitral Regurgitation

NEAL W. SALOMON, MD
EDWARD B. STINSON, MD, FACC*
RANDALL B. GRIEPP, MD
NORMAN E. SHUMWAY, MD, FACC

Stanford, California

Between October 1965 and April 1975, mitral valve replacement wa performed in 66 patients with myxomatous degeneration of the mitral valv ("floppy valve syndrome"). Operative mortality was 6 percent (four pa tients). Current evaluation was obtained for all patients; the averag postoperative follow-up interval for surviving patients was 3.5 years (rang 1 month to 9.9 years); the total duration of postoperative follow-up for a patients was 180 patient-years. Overall survival rates, calculated by th actuarial method, were 81, 68 and 50 percent, respectively, 1, 2 and years after mitral valve replacement.

Preoperative variables with a significantly adverse effect on patie survival included patient age greater than 50 years, New York Hea Association functional class IV, left ventricular end-diastolic pressur greater than 12 mm Hg and mean pulmonary arterial wedge pressur greater than 16 mm Hg. Support is advanced for the concept that mitr valve dysfunction associated with myxomatous degeneration constitute a broad spectrum of clinicopathologic involvement. Acute clinical an hemodynamic deterioration may often occur in the setting of chronic mitr valve dysfunction. Postoperative mortality is directly related to preo erative functional disability and hemodynamic evidence of impaired le ventricular function. Consideration should be given to earlier operativ intervention in patients with myxomatous mitral degeneration and mitr insufficiency before severe and probably irreversible impairment ventricular function occurs.

Myxomatous degeneration of the mitral valve ("floppy valve syndrome is one cause of acquired nonrheumatic mitral regurgitation. Its diagnos is based predominantly on gross anatomic and microscopic feature although characteristic clinical, echocardiographic and angiocard ographic findings may also accurately identify this lesion.[1–6] Usuall the valve leaflets and "anulus" appear stretched, redundant and gela inous in consistency, and the chordae tendineae are elongated, atte uated and often ruptured. Histologic examination of the valve leafle shows diffuse infiltration with characteristically staining acellul myxomatous tissue, fragmentation of the collagenous cusp fibrosa[7,8] a an absence of inflammatory changes.

The clinical and pathologic findings associated with myxomato degeneration of the mitral valve have been described in a few patients.[9] However, long-term survival and evaluation of patients requiring mitr valve replacement for myxomatous degeneration have not been w defined. We have therefore analyzed the late postoperative status a the influence of various preoperative variables on the long-term pro nosis in 66 patients who underwent replacement of myxomatous mitr valves at this center during a 10 year period.

From the Department of Cardiovascular Surgery, Stanford University Medical Center, Stanford, Calif. 94305. Manuscript received November 26, 1975, revised manuscript received February 9, 1976, accepted February 11, 1976.

* Established Investigator, American Heart Association.

Address for reprints: Edward B. Stinson, MD, Department of Cardiovascular Surgery, Stanford University Medical Center, Stanford, Calif. 94305.

Patients and Methods

Between October 1965 and April 1975 a total of 135 patients underwent mitral valve replacement for pure mitral regurgitation at Stanford University Medical Center. Patients with definitive etiologic diagnosis unrelated to myxomatous mitral valve degeneration were excluded from further consideration (for example, rheumatic heart disease, infective endocarditis, trauma, papillary muscle dysfunction or rupture secondary to coronary artery disease). The remaining cases in which the gross appearance of the mitral valve apparatus (as determined intraoperatively) presented the characteristic features of myxomatous mitral valve degeneration described were selected for detailed analysis. Sixty-six patients fulfilled this criterion. Microscopic examination of operative specimens was performed in 28 of the 66 cases; in all of these the diagnosis of myxomatous degeneration (acid mucopolysaccharide infiltration) was confirmed by special stains (Alcian blue, colloidial iron). Comparison of the groups with and without histologic documentation on the basis of clinical characteristics and postoperative outcome revealed no significant differences in any category.

Assessment of preoperative variables included review of clinical, radiographic, electrocardiographic and cardiac catheterization data; the variables that correlated significantly with operative outcome are discussed later. The average patient age was 58 years (range 11 to 80 years). Forty-eight patients were men. According to the 1964 New York Heart Association classification of preoperative disability, 18 patients were in class II, 30 in class III and 15 in class IV. Thirty-six patients had sinus rhythm, 27 had atrial fibrillation and 3 had other cardiac arrhythmias. The preoperative interval during which a systolic murmur was known to be present averaged 4 years but ranged widely (from 1 month to 50 years). Only of the 66 patients had a documented mid-systolic click by phonocardiography.

The results of preoperative cardiac catheterization in 49 patients were as follows: (1) average cardiac index at rest 2.1 ± 0.6 (standard error) liters/min per m^2; (2) average mean pulmonary arterial pressure 34.3 ± 12.4 mm Hg; (3) average pulmonary arterial wedge pressure 22.6 ± 7.6 mm Hg; (4) average *V* wave in pulmonary wedge recordings 40 ± 15 mm Hg; and (5) average left ventricular end-diastolic pressure 15.3 ± 5.9 mm Hg. Left ventriculography, performed in 39 patients, revealed severe mitral regurgitation (3 or 4 on a scale of 0 to 4) in all. Left ventricular function was classified as good in 34 patients, fair in 4 patients and poor in 1 patient. Coronary arteriography was not performed routinely in this series; however, only 2 of the 11 patients who underwent this procedure had significant occlusive coronary artery disease, and both underwent simultaneous aortocoronary saphenous vein bypass grafting and mitral valve replacement.

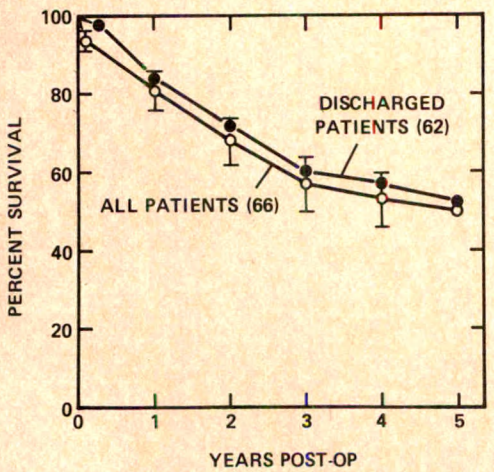


FIGURE 1. Five year postoperative (POST-OP) survival rates for all patients and for discharged patients only.

Operative technique: Standard techniques for cardiopulmonary bypass utilizing either a disc or disposable bubble-type oxygenator were employed. All operations were performed through a median sternotomy. The aorta was usually cross-clamped during excision of the valve and placement of sutures in the valve "anulus"; during this period (average 34 minutes, range 15 to 89 minutes) topical myocardial hypothermia was induced by continuous cooling with saline solution at 3 to 4° C.[11] During placement of sutures in the valve sewing rim, insertion of the valve and closure of the left atrial incision, coronary perfusion was usually reestablished. Venting of the left ventricle was accomplished with a T tube placed through the left atriotomy and across the valve until after ventricular defibrillation. There were no attempts at primary repair of the valve apparatus (plication, anuloplasty or reattachment of ruptured chordae). Starr-Edwards model 6120 valves were used in 38 patients, porcine aortic valve xenografts (Hancock) in 20[12] and stented aortic valve allografts in 8.[13]

Postoperative evaluation: Current follow-up evaluation of all discharged patients was obtained by direct contact with the patient or his physician, or both. Functional classification was assigned according to New York Heart Association criteria on the basis of current symptoms. The average follow-up interval for surviving patients was 3.5 years (range 1 month to 9.9 years), and the total duration of postoperative follow-up analysis for all patients in the study was 180 patient-years.

Results

Operative mortality: The overall operative mortality rate (less than 30 days) was 6.0 percent (four patients). One death was due to pulmonary embolism and one to cerebral infarction; two deaths were attributed to intraoperative technical error. There were no early postoperative deaths due to myocardial failure.

Late postoperative survival: Late postoperative survival rates, calculated with the actuarial method,[14] are shown in Figure 1. The survival rate at 5 years for all patients was 50 ± 8 percent, and for patients discharged from the hospital (operative survivors) 53 ± 8 percent.

Seven of the 21 late postoperative deaths were due to congestive heart failure; 5 were sudden and unexplained and 3 were caused by documented ventricular arrhythmias. Four deaths were attributed to a cerebrovascular accident; all four occurred in patients who had received a Starr-Edwards valve, but the cause (embolism) could be determined in only one case. The remaining two deaths were due to myocardial infarction and to an accident. No deaths could be related directly to hydraulic dysfunction of the valve substitute. In two of the five cases of sudden unexplained death, autopsy was performed and excluded mechanical valve dysfunction as a cause of death.

Valve failure: Valve failure occurred in six patients, and reoperation was required in five. The six cases of valve failure may be classified into two types: primary failure of the prosthesis (four cases), and perivalvular

leak (two cases). The first subgroup included three patients with progressive dysfunction of a stented allograft,[13] two of whom underwent successful reoperation utilizing a porcine xenograft; one patient underwent successful replacement of a porcine xenograft involved with infective endocarditis. The remaining patient in this subgroup had a minimal degree of allograft stenosis and regurgitation and was functionally limited (class II) when last seen.

The other two cases of valve failure were considered secondary to disruption of sutures in the myxomatous mitral "anulus," resulting in partial valve dehiscence. In both cases, reoperation was necessary to close perivalvular leaks.

Thromboembolism: Systemic thromboembolic episodes were diagnosed on the basis of any new postoperative neurologic defect developing suddenly (unless proved to be nonembolic) or an embolic occlusion of a peripheral artery. Fourteen thromboembolic episodes occurred postoperatively in 12 patients, 10 of whom had a Starr-Edwards prosthesis. All were receiving warfarin sodium at the time of embolization. Two of these patients died as a result of cerebral embolism.

The two remaining patients who sustained a thromboembolic episode had received tissue (allograft) valves. One had an immediate postoperative cerebrovascular accident after a degenerated calcified allograft valve was replaced with a porcine xenograft. Another had a transient neurologic defect several years after valve replacement with an aortic allograft. No thromboembolic episodes occurred in the 20 patients undergoing mitral valve replacement initially with porcine xenografts.

Correlates of patient survival: Statistical evaluation of the influence of various preoperative clinical and hemodynamic variables on postoperative survival was assessed by comparing survival curves after the entire group of patients had been dichotomized on the basis of a single variable.[15] A two-tailed significance level was assigned to the P values thus obtained. Variables evaluated included age, New York Heart Association functional classification, preoperatively documented coronary artery disease, previous myocardial infarction, cardiac catheterization and angiographic data, roentgenographic and echocardiographic data, presence or absence of ruptured chordae tendineae and prolapse of specific mitral leaflets.

Significantly adverse correlates of patient survival included: (1) patient age greater than 50 years, (2) New York Heart Association functional class IV (compared with class III or less), (3) left ventricular end-diastolic pressure greater than 12 mm Hg and (4) mean pulmonary arterial wedge pressure greater than 16 mm Hg. The highly significant impact of advanced functional disability (New York Heart Association class IV) on survival is illustrated in Figure 2, which indicates only a 40 ± 12 percent survival rate 2 years after operation. No significant correlation with survival was found with the following variables that might be considered to have a potential influence on the results of mitral valve replacement: cardiac index, pulmonary arterial pressures (mean and systolic), calculated pulmonary vascular resistance, the angiographic grade of mitral regurgitation, the preoperative duration of a known systolic murmur, ruptured chordae tendineae found at operation (62 percent of cases), preoperative cardiac rhythm or left atrial size by chest roentgenogram. Twenty of the 66 patients gave a history of dramatic and sudden onset of symptoms; in 17 of these (85 percent) ruptured chordae tendineae were noted at operation. No statistically significant correlation was found between specific mitral leaflet prolapse (anterior, posterior, or both) and (a) presence or absence of ruptured chordae tendineae, (b) preoperative functional class, (c) left ventricular end-diastolic pressure greater than 12 mm Hg, (d) pulmonary arterial wedge mean pressure greater than 16 mm Hg, or (e) postoperative survival.

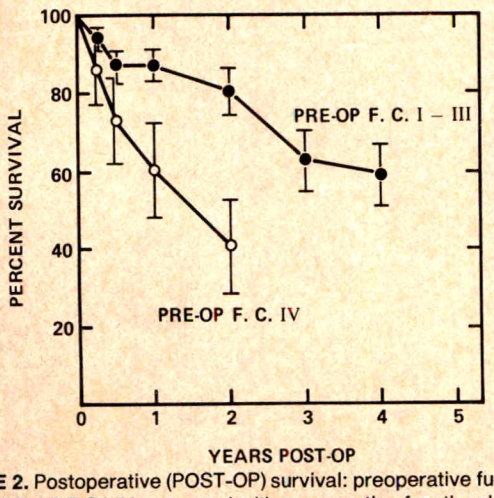


FIGURE 2. Postoperative (POST-OP) survival: preoperative functional class (PRE-OP F.C.) IV compared with preoperative functional classes I to III (New York Heart Association).

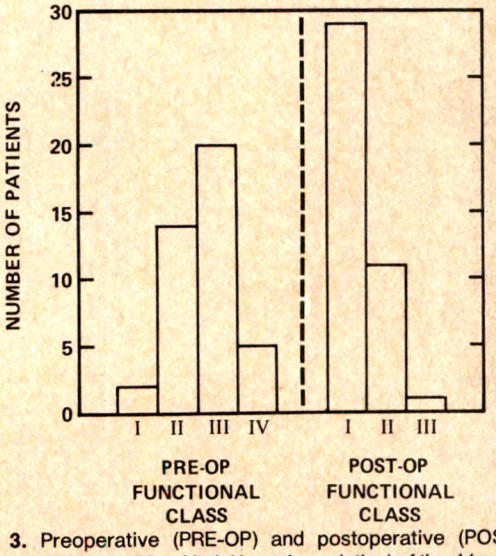


FIGURE 3. Preoperative (PRE-OP) and postoperative (POST-OP) functional classification (New York Heart Association) of the 41 currently surviving patients.



FIGURE 4. Photomicrograph of mitral valve leaflet demonstrating the loose myxomatous appearance of the degenerated portion of the valve. Note the minimal evidence of accompanying inflammation. (Hematoxylin-eosin ×125, reduced by 29 percent.)



FIGURE 5. Photograph of excised myxomatous mitral valve showing redundant and corrugated appearance of the valve leaflets.

Functional classification: Forty-one of the 66 patients in this series are alive, including the 5 patients who required repeat mitral valve replacement. The current functional status of surviving patients is contrasted with their preoperative functional status in Figure 3. Twenty-nine patients are in functional class I, 11 are in class II and 1 is in class III.

Discussion

Clinicopathologic Features

The surgical treatment of myxomatous degenerative valve disease was first emphasized by Read and his coworkers.[16,17] Although the mitral valve is almost always involved with myxomatous changes, some studies have shown that the proximal aorta and aortic valve may exhibit similar changes in addition to, or independent of, involvement of the mitral apparatus.[9] Despite many observations regarding clinical, pathologic, echocardiographic and genetic features[18–20] of myxomatous mitral valve disease, the etiology of this degenerative process remains obscure. Microscopic examination characteristically shows fibrous degeneration and replacement of affected valve tissue with acellular mucoproteinaceous (myxomatous) material (Fig. 4). The biochemical nature of this excess acellular ground substance has been variably classified as chondroitin sulfate C galactosamine,[9] sulfated mucopolysaccharide[21] or a protein-acid mucopolysaccharide complex.[22] It is unknown whether accumulation of this abnormal myxomatous material is due to a biochemical disorder of synthesis or degradation. Furthermore, it is not yet firmly established that the accumulation of abnormal amounts of myxomatous material is a primary event resulting in structural weakness of the involved valve apparatus or whether the myxomatous change represents a secondary response to abnormal mechanical stresses.[22]

Evidence that mitral valve dysfunction associated with myxomatous degeneration constitutes a broad spectrum of clinicopathologic involvement comes from several sources. It seems reasonably well established that similar pathologic changes may be present in the mitral leaflets of patients with the "click-murmur" syndrome, associated with prolapse or "billowing" of one or both mitral leaflets.[23–30] In the majority of such patients the functional consequences are relatively benign, although there appears to be a related predisposition to ventricular arrhythmias,[18,22] infective endocarditis[9,17,31] and rupture of chordae tendineae.[9,17,32] However, there is substantial evidence that progressively more serious derangement of mitral valve function, with or without rupture of chordae tendineae, may occur. For instance, Bittar and Sosa[27] described 14 patients with a "billowing" mitral valve and various degrees of mitral regurgitation; 3 patients with severe symptoms underwent mitral valve replacement and at operation exhibited typical gross features of myxomatous degeneration that was confirmed by histologic examination. Davis et al.[10] in a study of five patients who underwent mitral valve replacement for anatomically and pathologically documented myxomatous degeneration of the mitral valve and mitral insufficiency confirmed the probable progression of the process. The clinical data in our own series support both the chronicity of the "myxomatous mitral valve syndrome" in some patients (average duration of a known systolic murmur of 14 years) as well as the sudden symptomatic deterioration that may occur with the superimposition of chordal rupture (17 of 20 patients with acute onset of symptoms had chordal rupture at the time of operation).

Of some interest was the relative frequency of this lesion as a cause of pure functional mitral regurgitation. During a 9.5 year interval, 66 (49 percent) of 135 patients who underwent mitral valve replacement for pure mitral regurgitation were diagnosed as having degenerative mitral valve disease on the basis of gross and histologic features of the mitral valve tissue. This is a somewhat higher incidence rate than that of the only other reported large surgically treated series, in which Cooley et al.[32] documented a 23 percent incidence of degenerative mitral disease (50 patients) in patients undergoing mitral valve replacement for pure mitral regurgitation.

Relation to mitral valve prolapse syndrome: In a comprehensive review of the mitral valve prolapse-click-murmur syndrome, Jeresaty[3] provided substantial evidence to implicate myxomatous degeneration as the underlying pathologic process. Cases of myxomatous degeneration of the mitral valve may represent a continuous spectrum of clinical and functional manifestations. Cases with isolated mitral valve prolapse (usually confined to the posterior mitral leaflet)[3] or a "click-murmur syndrome" represent a mild form of myxomatous degeneration, associated with absent or only slight disability. However, those with holosystolic murmurs and gross mitral regurgitation represent more severe involvement, usually with prolapse of either the anterior or both leaflets, as illustrated in our series of solely operative cases (Fig. 5). Although it is clear that rupture of chordae tendineae may accelerate the functional consequences of myxomatous mitral valve degeneration, our operative experience indicates that redundancy and prolapse of the mitral leaflets alone may be sufficient to produce hemodynamically significant regurgitation. Indeed, in our study, although the diagnosis of ruptured chordae tendineae had been made in 58 of the 66 patients preoperatively, the diagnosis was documented at operation in only 41 cases. It therefore appears that myxomatous degeneration of the mitral valve apparatus can be implicated as a common, though not sole, cause of rupture of mitral chordae tendineae independent of "spontaneous" rupture of normal or rheumatically diseased chordae.

Factors Affecting Postoperative Survival

Specific operative morbidity related to myxomatous anular tissue was noted in two of our patients who had prosthetic valve dehiscence. Similar experiences have been previously reported.[17,32–34] The often inadequate fibrous mitral anular support and potential for prosthetic valve dehiscence noted in this condition may pose specific technical considerations at operation.

The late postoperative survival rates (53 ± 8 percent 5 year survival) in this series illustrate the relatively serious nature of this disorder. Although complete data regarding long-term postoperative evaluation of patients undergoing mitral valve replacement for either pure mitral regurgitation or specifically for myxomatous degeneration are not available from other centers, the survival rates in our series seem unusually low in comparison with the general experience for isolated mitral valve replacement. However, several studies have noted the significantly greater perioperative mortality and incidence of impaired ventricular function after mitral valve replacement for pure mitral regurgitation as compared with replacement for isolated stenosis or mixed functional lesions.[35,36] Postoperative attrition was especially prominent in patients with advanced preoperative functional disability and left ventricular failure, as evidenced by the statistically significant adverse correlates of patient survival. Furthermore, the majority of late deaths were due to congestive heart failure or were sudden and unexplained.

Although such features are not unique to patients undergoing mitral valve replacement for myxomatous disease they are consistent with the myocardial abnormalities that have been elucidated in this disorder. For example, the propensity to both mild and life-threatening arrhythmias in this condition has been documented previously.[18,22] These considerations and the significantly superior postoperative survival experience and symptomatic responses of patients without severe left ventricular failure suggest that consideration should be given to performing mitral valve replacement earlier in the course of patients with progressive symptoms, before severe and probably irreversible impairment of ventricular performance has occurred.

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Hemodynamic Effects of Nitroglycerin Ointment in Congestive Heart Failure

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The hemodynamic effects of nitroglycerin absorbed transcutaneousl from an ointment base were determined in 10 patients with chronic con gestive heart failure (9 with ischemic heart disease and 1 with cardio myopathy). The response was characterized by a decrease in pulmonar capillary wedge pressure from an average of 30 to 19 mm Hg, and an in crease in cardiac index from 1.7 to 2.2 liters/min per m^2, with concomitar decreases in systemic and pulmonary vascular resistance and an increas in venous capacitance. Mean arterial pressure decreased from 85 to 8 mm Hg, and heart rate remained unchanged. The hemodynamic effect persisted for 3 to 6 hours. These results indicate that nitroglycerin ointmer is a hemodynamically potent vasodilating agent with potential value i the therapy of congestive heart failure.

Drugs that cause dilatation of peripheral vessels have been shown to b extremely effective in the therapy of both acute and chronic congestiv heart failure.[1–13] Despite the theoretical advantages of vasodilators wit regard to myocardial oxygen supply and demand,[14,15] and the substanti hemodynamic improvement the drugs induce, practical problems exis in clinical use. Nitroprusside and phentolamine given intravenousl require precise invasive hemodynamic monitoring because of their rapi and profound cardiovascular actions. Sublingually administered n troglycerin and isosorbide dinitrate do not require hemodynamic mor itoring, but their duration of action is short.[10,12] Orally administere isosorbide dinitrate has a longer duration of action and may be a mor practical therapeutic agent.[13]

Nitroglycerin ointment has been demonstrated to produce a sustaine enhancement of exercise capacity for more than 3 hours.[16] This stud was designed to determine if nitroglycerin ointment might provide beneficial and prolonged hemodynamic effect in patients with chroni congestive heart failure.

Methods

Ten patients, seven male and three female, ranging in age from 52 to 75 year were studied in the Cedars-Sinai Medical Center Myocardial Infarction Researc Unit. Descriptive clinical data are shown in Table I. All 10 patients had sever congestive heart failure, defined by the symptoms of dyspnea on minima exertion and moderate to severe pulmonary congestion by both radiographi and physical criteria. At the time of study all patients had a mean pulmonar capillary wedge pressure of more than 23 mm Hg. Nine patients had athero sclerotic heart disease, and one had primary myocardial disease. One patien had hemodynamically severe mitral insufficiency.

All hemodynamic recordings were made with the patient in the supine posi tion. Arterial pressure was monitored continuously through a 20 gauge cathete inserted into the radial artery. Right atrial, pulmonary arterial and pulmonar capillary wedge pressures and cardiac output assessed by thermodilution tech nique were recorded with a balloon-tipped flow-directed triple lumen cathe ter.[17,18] Venous capacitance was measured in six patients by the equilibriur method, using a mercury rubber strain gauge and a venous occlusion pressur

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of 30 mm Hg.[19] Hemodynamic variables were calculated as follows:

$$CI = CO/BSA \text{ in liters/min per } m^2$$
$$SVI = SV/BSA \text{ in ml/beat per } m^2$$
$$SWI = SVI \times (\overline{AP} - \overline{PCP}) \times 0.144 \text{ in gm/beats/m}^2$$
$$SVR = 80\ (\overline{AP} - \overline{RA})/CO \text{ in dynes sec cm}^{-5}$$
$$PVR = 80\ (\overline{PA} - \overline{PCP})/CO$$

where CI = cardiac index; CO = cardiac output; BSA = body surface area; SVI = stroke volume index; SWI = stroke work index; $\overline{AP}$ = mean arterial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; $\overline{PCP}$ = mean pulmonary capillary wedge pressure; $\overline{PA}$ = mean pulmonary artery pressure; and $\overline{RA}$ = mean right atrial pressure.

Previous medications were discontinued on the day of the study. After control hemodynamic data were recorded, nitroglycerin ointment (Nitrol®, Kremers-Urban) was applied to the upper abdomen. The ointment contains 5 mg of nitroglycerin in each 0.4 inch (12.5 mg per inch). It is supplied in tubes and dosage is measured in inches of ointment applied to the patient. The dose employed in this study ranged from 1.5 to 4 inches (18.75 to 50 mg of nitroglycerin). The dose chosen was based upon the clinical assessment of the magnitude of congestive heart failure as reflected by physical examination and chest X-ray findings plus the initial hemodynamic measurements (blood pressure, cardiac index and pulmonary capillary wedge pressure). The ointment was spread on the skin in a square, whose sides were equal to the length of the dose expressed from the tube, and covered with applicator paper supplied with the medication. All hemodynamic measurements were then repeated at 20 minute intervals until the peak effect was observed, and then every 30 minutes until all hemodynamic measurements returned to baseline levels.

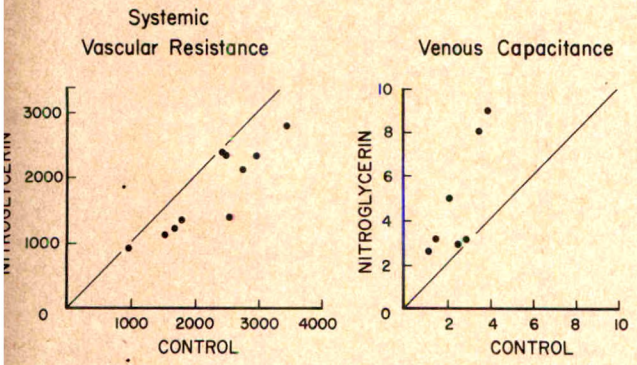


FIGURE 1. Changes in systemic vascular resistance (dynes sec cm^{-5}) and venous capacitance (cc/100 cc) after administration of nitroglycerin ointment. In all patients, systemic vascular resistance decreased (mean 30 percent) and venous capacitance increased (mean 92 percent).

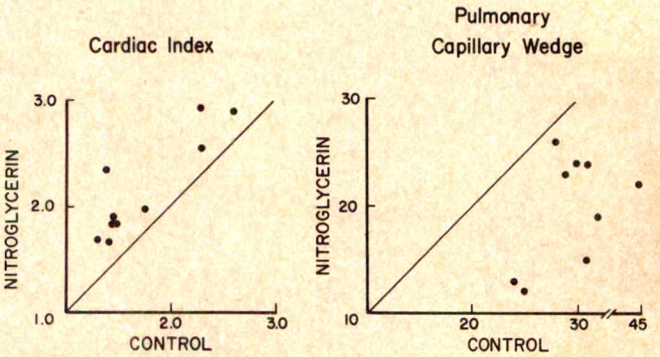


FIGURE 2. Changes in pulmonary capillary wedge pressure (mm Hg) and cardiac index (liters/min per m^2) after administration of nitroglycerin ointment. In all patients pulmonary capillary wedge pressure decreased (mean 37 percent) and cardiac index increased (mean 24 percent).

TABLE I

Clinical Data in 10 Cases

Case No.	Age (yr) Sex	Diagnosis	Previous Therapy	Comments
1	75 M	CAD (MI X 2)	Furosemide, isosorbide dinitrate, quinidine	MR, TR, bilateral pleural effusion
2	54 F	Idiopathic congestive cardiomyopathy	Digoxin, furosemide, isosorbide dinitrate	MR, TR, LBBB
3	68 M	CAD (MI X 2), hypertension	Digoxin, furosemide	
4	72 M	CAD (MI X 3), MR	Digoxin, furosemide, quinidine	Severe MR
5	58 M	CAD (MI X 2)	Digoxin, furosemide, isosorbide dinitrate	
6	74 F	CAD (MI X 3)	Digoxin, ethacrinic acid	Pleural effusion, severe peripheral edema
7	59 M	CAD (MI X 4), CABG, aneurysmectomy	Furosemide, isosorbide dinitrate, quinidine	
8	68 M	CAD (MI X 2)	Digoxin, furosemide, quinidine, Aldomet®	
9	65 F	CAD (MI X 1)	Digoxin, furosemide	Severe peripheral edema and ascites
10	52 M	CAD (MI X 1), diabetes mellitus	Digoxin, furosemide	

CABG = postoperative state after coronary artery bypass graft; CAD = coronary artery disease; LBBB = left bundle branch block; MI = myocardial infarction; MR = mitral regurgitation; TR = tricuspid regurgitation.

Results

For the purpose of analysis, the maximal change in hemodynamic variables for each patient was defined as occurring at the time of maximal increase in cardiac output. The vascular response to nitroglycerin ointment (Table II) was characterized by a decrease in systemic resistance with an increase in venous capacitance (Fig. 1). Concomitant with these vascular changes, pulmonary capillary wedge pressure decreased by an average of 37 percent (30 to 19 mm Hg), whereas cardiac index increased 24 percent (1.7 to 2.2 liters/min per m^2) (Fig. 2), stroke volume index increased 23 percent and stroke work index 27 percent. In Patient 10, the stroke volume index did not increase. This patient had unusually low initial levels of systemic vascular resistance and mean arterial blood pressure. Although the magnitude of the hemodynamic responses was variable, the direction of these responses was consistent in all patients.

Hemodynamic changes were first noted 20 minutes after application of the ointment. The peak action occurred 1 to 4 hours after application, and the greatest increase in cardiac index for the entire group occurred 3 hours after application (Fig. 3). The duration of action ranged from 3 to 6 hours; it was 4 to 5 hours in five cases. In the patient with mitral regurgitation (Patient 4), nitroglycerin ointment resulted in a significant increase in forward stroke index and a marked reduction in the peak *V* wave pressure and mean pulmonary capillary wedge pressure (Fig. 4).

Discussion

Since the report of the hemodynamic benefits of phentolamine in patients with congestive heart failure,[20] a variety of drugs with a vasodilator action have been shown to be of exceptional clinical efficacy in this condition. Sodium nitroprusside has been effective in pa-

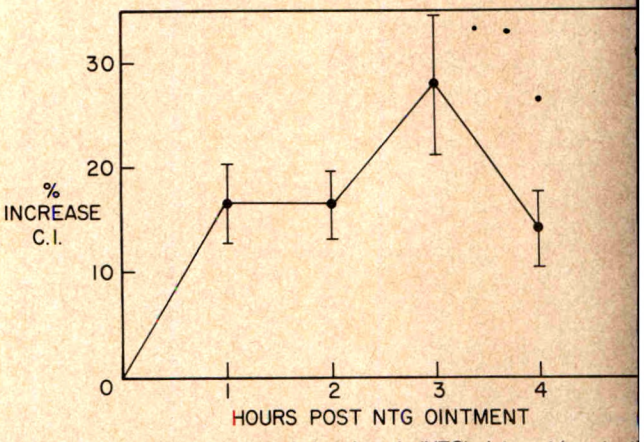


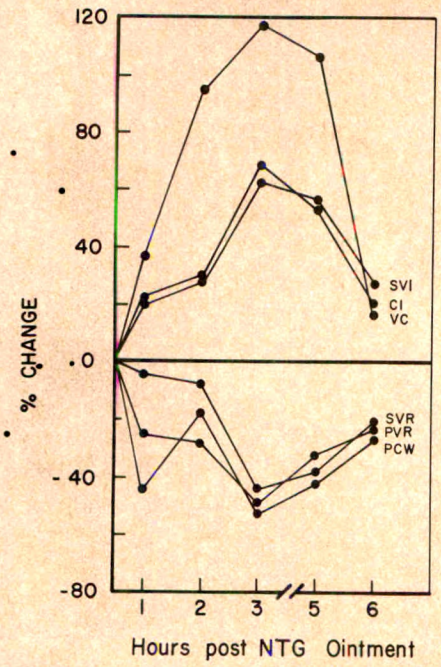
FIGURE 3. Duration of action of nitroglycerin (NTG) ointment (see text). Bars indicate standard errors. C.I. = cardiac index.

TABLE II

Hemodynamic Effects of Nitroglycerin Ointment In Congestive Heart Failure

Case no.		HR	Pressures (mm Hg) $\overline{AP}$	$\overline{PCW}$	$\overline{RA}$	CI	SVI	SWI	SVR	PVR	VC
1	C	74	90	29	7	1.41	19	22	3482	538	2.88
	N	73	83	23	4	1.65	23	24	2724	430	3.14
2	C	111	90	25	17	1.47	13	13	2758	255	2.54
	N	98	76	12	9	1.83	19	20	2157	218	2.96
3	C	68	92	32	13	1.75	26	25	2511	540	
	N	67	93	19	7	1.97	29	29	2323	499	
4	C	83	83	31	11	1.38	17	16	2522	665	3.56
	N	86	70	15	3	2.34	27	27	1392	394	8.10
5	C	68	84	24	3	2.28	34	37	1452	233	4.02
	N	72	83	13	1	2.91	40	51	1150	112	9.07
6	C	79	76	30	16	1.28	16	16	2432	588	
	N	79	84	24	7	1.68	21	26	2373	462	
7	C	81	85	45	22	1.45	18	12	1789	437	1.14
	N	84	77	22	15	1.89	23	21	1342	346	2.65
8	C	60	90	25	6	2.29	38	52	1627	251	2.21
	N	57	76	12	4	2.57	45	54	1223	735	5.07
9	C	72	105	31	19	1.45	20	32	2993	490	1.5
	N	74	97	24	13	1.83	25	36	2387	426	3.2
10	C	101	64	28	6	2.6	26	14	988	102	
	N	110	66	26	5	2.88	26	15	926	106	
Mean	C	79	85	30	12	1.7	23	24	2255	410	2.6
	N	80	80	19	7	2.2	28	30	1796	313	4.9
% Change		+0.4%	−6%	−37%	−43%	+24%	+23%	+27%	−20%	−24%	+92%
P value		NS	<0.025	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.0

$\overline{AP}$ = mean arterial pressure; C = control state; CI = cardiac index (liters/min per m^2); HR = heart rate (beats/min); N = after administration nitroglycerin ointment; NS = not significant; *P* = probability; $\overline{PCW}$ = mean pulmonary capillary wedge pressure; $\overline{PVR}$ = pulmonary vascular resistance (dynes sec cm^{-5}); $\overline{RA}$ = mean right atrial pressure; SVI = stroke volume index (ml/min per m^2); SVR = systemic vascular resistance (dynes sec cm^{-5}); SWI = stroke work index (g-m/beat per m^2); VC = venous capacitance (cc/100 cc).



IGURE 4. Hemodynamic changes after administration of nitroglycerin ITG) ointment in a patient with severe mitral regurgitation. CI = cardiac ıdex; PCW = mean pulmonary capillary wedge pressure; PVR = ulmonary vascular resistance; SVI = stroke volume index; SVR = ystemic vascular resistance; VC = venous capacitance.

ents with acute left ventricular failure, acute and hronic mitral regurgitation and chronic congestive eart failure.[2–7] Isosorbide dinitrate administered ıblingually to patients with chronic congestive heart ıilure has been shown to increase cardiac output and) diminish left ventricular filling pressure.[12] Our study ıdicates that the administration of nitroglycerin intment to patients with chronic convestive heart ıilure results in a decrease in left ventricular filling ressure and an increase in cardiac output associated ith a reduction in peripheral vascular resistance and ı increase in venous capacitance.

Mechanism of hemodynamic effects: The relative ffects on the arteriolar and venular beds in the presence of heart failure are probably of critical importance in determining the hemodynamic effect of the drug.[1] In heart failure, agents that reduce systemic vascular resistance decrease afterload and increase ejection fraction, resulting in an increased stroke volume, whereas an isolated increase in venous capacitance decreases preload, resulting in a decrease in pulmonary capillary wedge pressure and often no change or a decrease in stroke volume. Therefore, to have a substantial effect on stroke volume, a vasodilator must decrease systemic vascular resistance.

Nitroglycerin has an effect on both preload and afterload.[21–26] Previous studies have demonstrated a decrease in regional forearm resistance and total peripheral resistance after its administration.[21,22] Gold et al.[10] observed a decrease in peripheral vascular resistance and an increase in cardiac output after sublingual administration of nitroglycerin to three patients with refractory left ventricular failure. Similar results were observed by Cohn et al.[9] in one patient with severe congestive heart failure. Our study supports these previous observations and indicates that nitroglycerin ointment has a substantial effect on both peripheral vascular resistance and venous capacitance.

Therapeutic implication: Vasodilating agents may be of value in the long-term management of congestive heart failure.[9] For practical use, such agents must have both substantial hemodynamic effects and an adequate duration of action. Sublingually administered isosorbide dinitrate and nitroglycerin have significant hemodynamic effects, but their duration of action is short.[10,12] In contrast, both orally administered isosorbide nitrate[13] and percutaneously absorbed nitroglycerin have a substantially greater duration of action. These agents, therefore, appear to be more practical for long-term therapy. On the basis of its hemodynamic effectiveness and duration of action, percutaneously absorbed nitroglycerin has potential value in the treatment of congestive heart failure due to ischemic heart disease. Although our study evaluated only the effects of short-term administration of nitroglycerin ointment, the results suggest that further clinical trials are indicated to determine its efficacy in the long-term therapy of congestive heart failure.

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Nitroglycerin Ointment in Acute Myocardial Infarction

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The hemodynamic effects of nitroglycerin ointment were studied in 22 patients with acute myocardial infarction. Control measurements were obtained and observations were made over the ensuing 240 minutes. There was no change in heart rate, cardiac index or stroke index. Ninety minutes after application of the ointment, peak decrements were evident in mean arterial pressure (from 100 to 88 mm Hg) ($P < 0.001$), pulmonary capillary wedge pressure (from 19 to 13 mm Hg) ($P < 0.001$), right atrial pressure (from 8 to 5 mm Hg) ($P < 0.001$) and heart rate × systolic blood pressure (from 1,155 to 1,044 mm Hg/min × 10^{-1}) ($P < 0.02$); significant changes were still present at 240 minutes. Total peripheral resistance decreased maximally from 19.8 to 17.2 units ($P < 0.02$); the transmyocardial gradient (arterial diastolic − pulmonary capillary wedge pressure) did not decrease during the study.

These data indicate that nitroglycerin ointment improves cardiac performance in patients with acute myocardial infarction while reducing the determinants of myocardial oxygen consumption and preserving the transmyocardial gradient for coronary blood flow.

Vasodilator therapy in acute myocardial infarction has been the subject of intensive recent investigation. This development is in part a result of experimental studies indicating that favorable alterations in the determinants of myocardial oxygen consumption may reduce ischemic injury and that reduction in afterload may be associated with improved cardiac performance. To date these studies[1–7] have involved assessment of intravenously administered sodium nitroprusside, trimethaphan, phentolamine and intravenously and sublingually administered nitroglycerin. Topical administration of nitroglycerin in ointment form was originally suggested as a useful therapeutic measure for angina pectoris[8] and has recently been shown to provide protection against exercise-induced angina for up to 3 hours.[9,10] Its ease of administration and potential for sustained action suggested that it might be useful in the management of acute myocardial infarction. Accordingly we investigated its hemodynamic effects in the early period after acute myocardial infarction.

Methods

Case material: Twenty-two patients in the Connell Coronary Care Unit of the Kingston General Hospital, Ontario, were studied in the first 24 hours after acute myocardial infarction. Nineteen patients were male and three were female; the average age was 56 years (range 35 to 70 years). In all patients the infarction was confirmed with serial electrocardiographic and serum enzyme determinations. The site of the infarction was anterior in 15 and inferior in 7. Peak serum glutamic oxaloacetic transaminase (SGOT) levels in milli-international units per milliliter were 250 or less in 3, between 250 and 500 in 9 and 500 or more in 10 patients (normal range 10 to 50). Peak creatine phosphokinase (CPK) levels in milli-international units per milliliter were 1,000 or less in 7, between 1,000

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TABLE I

Summary of Hemodynamic Response to Nitroglycerin Ointment in 22 Cases

	HR	MAP	PCWP	RAP	CI	SI	HR × SBP	TPR	LVSWI	TMG
C	87 ± 3	100 ± 4	19 ± 1	8 ± 1	2.6 ± 0.1	30.5 ± 1.8	1155 ± 49	19.8 ± 1.3	33.6 ± 2.9	59.2 ± 3.0
30′	87 ± 4	97 ± 4	16 ± 1	6 ± 1	2.5 ± 0.1	29.9 ± 2.0	1113 ± 59	19.4 ± 1.3	32.5 ± 3.0	62.4 ± 3.1
60′	87 ± 3	91 ± 3	14 ± 1	6 ± 1	2.6 ± 0.1	30.6 ± 1.6	1070 ± 51	18.0 ± 1.0	32.1 ± 2.5	60.2 ± 3.0
90′	87 ± 4	88 ± 3	13 ± 1	5 ± 1	2.6 ± 0.1	30.9 ± 2.2	1044 ± 49	18.0 ± 1.2	31.9 ± 2.7	58.8 ± 2.9
120′	88 ± 4	88 ± 3	14 ± 1	5 ± 1	2.6 ± 0.1	31.4 ± 2.6	1054 ± 45	17.5 ± 1.1	32.4 ± 3.3	58.1 ± 3.1
240′	86 ± 4	88 ± 3	14 ± 1	6 ± 1	2.5 ± 0.1	30.8 ± 1.9	1030 ± 55	17.2 ± 1.0	31.5 ± 2.8	59.2 ± 3.2
P values										
C vs. 30′	NS	NS	<0.001	<0.001	NS	NS	NS	NS	NS	<0.01
C vs. 60′	NS	<0.001	<0.001	<0.001	NS	NS	NS	<0.02	NS	NS
C vs. 90′	NS	<0.001	<0.001	<0.001	NS	NS	<0.02	<0.02	NS	NS
C vs. 120′	NS	<0.001	<0.001	<0.001	NS	NS	<0.025	<0.05	NS	NS
C vs. 240′	NS	<0.001	<0.001	<0.001	NS	NS	<0.05	<0.02	NS	NS

All values expressed as mean ± standard error.
C = control; CI = cardiac index (liters/min per m²); HR = heart rate (beats/min); HR × SBP = heart rate × systolic blood pressure (mm Hg min × 10^{-1}); LVSWI = left ventricular stroke work index (g-m/m²); MAP = mean arterial pressure (mm Hg); NS = not significant; *P* = probability; PCWP = pulmonary capillary wedge pressure (mm Hg); RAP = right atrial pressure (mm Hg); SI = stroke index (ml/beat per m²); TMG = transmyocardial gradient (mm Hg); TPR = total peripheral resistance (units).

and 2,000 in 6 and 2,000 or more in 9 patients (normal range 0 to 188).

The hemodynamic criterion for admission to this study was the presence of "hypertension" as defined by a mean arterial pressure of 105 mm Hg or more, or a pulmonary capillary wedge pressure of 15 mm Hg or more (or both). The criterion was not met in Case 2, but this patient was included in the study group because the alterations in his hemodynamic status were directionally similar to those of the rest of the group.

Hemodynamic measurements: Instrumentation was performed after the patients gave informed consent. A thermistor Swan-Ganz catheter was passed from an antecubital vein to the pulmonary artery with electrocardiographic and pressure monitoring. A Teflon® cannula was placed in the radial artery. Right atrial and pulmonary arterial pressures, pulmonary capillary wedge pressure obtained by balloon occlusion and systemic arterial pressure were monitored and cardiac output was measured by the thermal dilution technique with injection of 10 ml of ice-cold 5 percent dextrose in water into the right atrium. Pressure and output data were displayed and recorded on a VR 6 Electronics for Medicine recorder, and output curves were computed electronically on an Edwards' cardiac output computer.

Derived calculations were performed using the formulas: SV = CO/HR; TPR = (MAP − RA)/CO; HR × SBP; TMG = ART_d − PCW, where SV = stroke volume in ml/beat, RA = right atrial pressure in mm Hg, CO = cardiac output in liters/min, HR = heart rate in beats/min, TPR = total peripheral resistance in units, MAP = mean arterial pressure in mm Hg, HR × SBP = heart rate × systolic blood pressure in mm Hg/min × 10^{-1}, TMG = transmyocardial gradient in mm Hg obtained by subtracting the pulmonary capillary wedge pressure from the arterial diastolic pressure. Statistical analysis was performed using Student's *t* test.

Protocol: No patient received cardiotonic agents during the study period, but two patients were receiving an infusion of lidocaine at a constant rate. Observations were made during a control period of 15 to 20 minutes during which the cardiac output was determined at least in duplicate. Nitroglycerin ointment, 2 percent (Nitrol, Kremers-Urban Company, Milwaukee, Wisc.) was then applied in a dose of 0.5 to 1.5 inches (1.27 to 3.81 cm) over a 6 by 6 inch (15.24 cm²) area on the flank or chest. The ointment was covered with plastic wrap and the edges secured with paper tape. A 1 inch (2.54 cm ribbon extruded from the manufacturer's tube contains 12.4 mg of nitroglycerin.

Complete hemodynamic data were obtained 30, 60, 90, 12(and 240 minutes after the application of nitroglycerin oint ment. Observations made in 12 patients 15 minutes after ap plication of the ointment revealed an effect on dynamics i 4 patients. In six patients additional observations were mad 300 minutes after the application of ointment, and in on patient (Case 20) observations were made at 380 minutes. I 10 patients data were also obtained 30 to 60 minutes afte removal of the ointment.

Results

Hemodynamic effects: The hemodynamic data ar summarized in Table I. Table II shows for each patien the changes in arterial pressure, pulmonary capillar wedge pressure and cardiac index before and after ap plication of the ointment. Because the peak effect oc curred between 60 and 90 minutes and the duration c action was sustained through 240 minutes, the dat obtained 30 and 180 minutes after application ar omitted. The dose of nitroglycerin ointment applied t each patient is also indicated in Table II; this dose wa to some extent selected empirically. The one patier (Case 18) who received 0.5 inch of ointment had pre viously been receiving nitroglycerin intravenously an had had a favorable hemodynamic response with th small dose of 15 μg/min. The importance of dose sele tion is also illustrated by Case 7. This patient had (aft initial study at a dose of 1 inch [2.54 cm] documente in Table II) a second study at a smaller dose of 0.75 inc and was followed up for 90 minutes. The latter stuc indicated a reduction in pulmonary capillary wedg pressure from 23 to 15 mm Hg and in mean arteri pressure from 110 to 95 mm Hg without the decrease cardiac index observed during the initial study. Sim larly, Patient 10, whose response to nitroglycerin oin ment was the smallest in the group, responded to i travenous administration of nitroglycerin at a rate 59 μg/min with a reduction in pulmonary capilla

TABLE II

Individual Hemodynamic Response Before and After Application of Nitroglycerin Ointment

Case no.	Dose (inch [cm])	Arterial Systolic Pressure (mm Hg)						Arterial Diastolic Pressure (mm Hg)						Mean Arterial Pressure (mm Hg)						Pulmonary Capillary Wedge Pressure (mm Hg)						Cardiac Index (liters/min per m²)					
		C	60′	90′	240′	300′	A	C	60′	90′	240′	300′	A	C	60′	90′	240′	300′	A	C	60′	90′	240′	300′	A	C	60′	90′	240′	300′	A
1	1 (2.54)	180	183	...	...	...	...	90	87	...	...	...	...	120	113	...	...	...	...	15	13	...	...	...	...	3.0	3.0	...	...	...	...
2	1 (2.54)	145	136	140	155	...	155	68	64	63	70	...	70	95	80	82	88	...	88	12	7	6	7	...	11	2.6	2.6	2.6	2.9	...	...
3	1 (2.54)	105	102	96	100	107	110	65	64	60	63	66	65	75	75	74	73	80	80	29	23	20	17	21	25	2.3	2.5	2.6	2.3	2.4	2.3
4	0.75 (1.91)	160	142	125	136	138	...	80	78	68	74	78	...	108	100	85	98	99	...	12	8	4	9	9	...	...	...	...	...	...	...
5	1 (2.54)	125	102	...	118	...	118	76	66	...	70	...	70	89	75	...	83	...	85	23	19	...	14	...	21	2.7	2.4	...	2.8	...	2.7
6	1 (2.54)	106	90	...	...	...	...	62	60	...	...	...	78	78	67	...	...	...	...	18	7	...	...	...	...	2.0	1.8	...	...	...	...
7	1 (2.54)	151	118	120	134	...	142	97	74	78	77	...	84	119	83	88	100	...	100	26	11	15	15	...	18	3.0	2.4	2.2	2.7	...	2.8
8	1 (2.54)	102	91	79	76	...	...	54	55	49	50	...	...	69	65	60	61	...	...	21*	18*	15*	19*	...	...	2.0	2.0	2.0	2.0	...	...
9	1.5 (3.8)	176	139	140	124	150	...	100	90	90	80	90	...	120	106	107	95	110	...	24*	20*	16*	18*	19*	...	2.2	2.5	2.6	2.2	2.2	...
10	1 (2.54)	104	103	107	107	...	...	68	66	73	73	...	...	82	82	85	83	...	...	32	31	30	32	...	...	1.9	2.2	2.2	2.1	...	...
11	0.75 (1.91)	172	158	150	118	...	125	93	82	75	58	...	60	125	108	98	75	...	78	15	9	8	8	...	13	2.2	2.0	2.0	1.4	...	1.6
12	1.25 (3.18)	110	128	115	...	...	...	73	76	67	...	...	...	87	97	82	...	...	...	21	20	16	...	...	...	2.9	3.3	2.8	...	...	...
13	1 (2.54)	160	158	150	157	...	168	96	98	74	96	...	100	126	117	112	108	...	125	19	4	2	7	...	15	2.8	2.5	2.2	2.7	...	2.5
14	1 (2.54)	105	95	85	90	87	95	68	63	58	63	62	67	80	76	65	70	70	76	23	20	17	17	16	21	2.8	2.2	2.4	2.7	2.3	2.0
15	0.75 (1.91)	134	135	133	127	...	...	76	75	75	73	...	...	98	94	95	91	...	...	18	13	14	11	...	...	3.0	2.9	2.8	2.7	...	...
16	0.75 (1.91)	118	110	118	107	106	...	79	77	82	72	73	...	95	90	93	83	84	...	17	10	10	10	13	...	1.5	1.9	1.8	2.1	2.0	...
17	0.75 (1.91)	148	98	108	...	...	...	97	68	68	...	...	...	117	85	90	...	...	...	27	10	15	...	...	...	2.6	2.5	2.5	...	...	...
18	0.5 (1.27)	123	120	118	112	...	...	72	74	72	70	...	...	90	90	87	83	...	...	18	12	14	13	...	...	2.7	2.7	3.2	2.7	...	...
19	1 (2.54)	125	126	124	122	120	120	76	74	74	76	72	70	96	92	90	90	87	88	16	9	8	9	11	13	2.9	3.3	3.1	2.9	2.7	...
20	0.75 (1.91)	135	136	127	129	133†	131	84	80	72	76	72†	80	104	99	92	94	95†	96	20	17	15	15	15†	19	2.5	2.7	3.1	2.9	2.7†	...
21	0.75 (1.91)	155	135	146	155	...	150	95	88	90	98	...	95	120	105	105	115	...	113	19*	16*	13*	18*	...	20*	3.2	3.2	2.8	3.1	...	3.2
22	0.75 (1.91)	126	128	127	125	...	...	82	76	75	77	...	...	100	95	88	94	...	...	22	13	8	13	...	...	3.1	3.2	3.0	3.3	...	...

* Pulmonary arterial diastolic pressure.
† Data obtained 380 minutes after application of ointment.
A = 30 to 60 minutes after removal of nitroglycerin ointment; C = control.

wedge pressure to 19 mm Hg without significant change in mean arterial pressure or cardiac index.

Table II also demonstrates persistence of effect through 300 minutes in six patients and through 380 minutes in a seventh patient (Case 20). The data obtained after removal of the ointment indicate a return toward control values.

Figure 1 displays the changes observed in the hemodynamic measurements in the total group. No change was seen in heart rate throughout the study, and mean arterial pressure decreased gradually from 100 to a minimum of 88 mm Hg at 90 minutes and remained at that level. A similar change was evident in pulmonary capillary wedge pressure, which decreased maximally at 90 minutes from 19 to 13 mm Hg and thereafter began to increase gradually. Right atrial pressure decreased gradually from 8 to a minimum of 5 mm Hg at 90 minutes and returned to 6 mm Hg by 240 minutes. No change was evident in cardiac index, stroke index or stroke work index. Heart rate-systolic blood pressure product decreased significantly at 90 minutes and remained at this level throughout the balance of the study. Total peripheral resistance decreased significantly at 60 minutes and remained reduced throughout the study. Transmyocardial gradient increased significantly at 30 minutes, but decreased to control level at 60 minutes and remained at this level throughout the study. This change reflects the fact that approximately 50 percent of the overall reduction in pulmonary capillary wedge pressure had occurred 30 minutes after application whereas at this time only a small reduction in mean arterial pressure was observed.

Untoward effects: Three studies had to be terminated prematurely. In Case 4 the patient had hypotension 55 minutes after the application of 1.5 inches of ointment and the study was terminated with elevation of the legs and removal of the ointment. Blood pressure was rapidly restored to normal and the study was repeated 12 hours later with 50 percent of the original dose. The initial dose in this case was the largest used in the study group and this patient was one of the first to be studied. Subsequently a dose of 0.75 or 1 inch was used initially; the larger dose was generally used in patients with greater elevation of either mean arterial pressure or pulmonary capillary wedge pressure. In Case 6 the study was terminated because of hypotension associated with weakness 90 minutes after application of the ointment (blood pressure reduced to 75/40 mm Hg). In Case 17 the study was terminated when the patient who was receiving lidocaine therapy for ventricular arrhythmias during the study, required supplemental procainamide therapy after the 90 minute observations. Although the mean arterial pressure of Patient 8 decreased from 69 to 60 mm Hg, there were no symptoms of ischemia or poor peripheral perfusion, and the cardiac output was preserved at a lower level of pulmonary capillary wedge pressure.

Discussion

Vasodilator therapy has been shown to affect favorably the immediate clinical and hemodynamic status

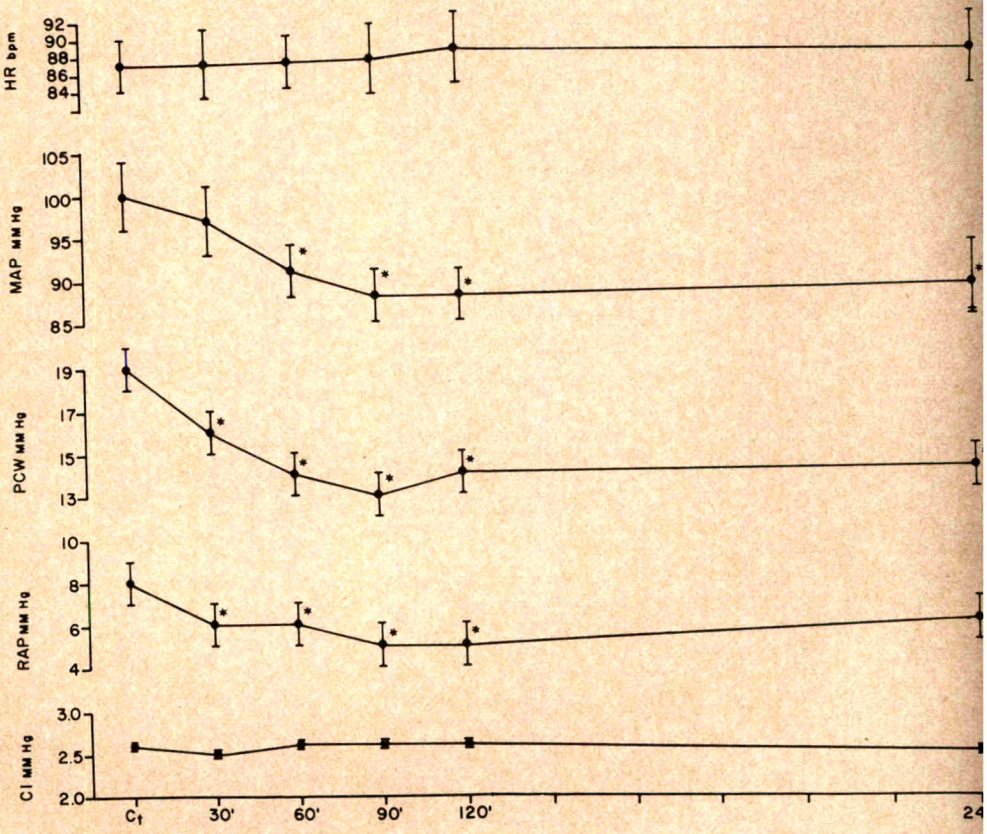


FIGURE 1. Changes in heart rate (HR), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCW), right atrial pressure (RAP) and cardiac index (CI) before and 30 to 240 minutes after application of nitroglycerin ointment. The plotted points represent mean values ± standard error for 22 patients. Points marked with an asterisk indicate a statistically significant change from the control (C_t) value. bpm = beats per minute.

f patients with acute myocardial infarction. There is lso recent evidence to suggest that such interventions nay reduce the extent of ischemic injury.[3] Most studies o date have employed either nitroprusside or nitro-lycerin although other agents have been utilized. A previous study[6] of nitroprusside and intravenously dministered nitroglycerin in patients with acute nyocardial infarction indicated that nitroglycerin leads o a greater reduction in pulmonary capillary wedge ressure than does nitroprusside, presumably because t has a greater pooling effect on the venous capacitance essels. The nitroglycerin administered during that tudy required time-consuming preparation, including entrifugation, decanting and refrigeration. The ready vailability, ease of administration and apparent sus-ained action of nitroglycerin ointment suggested to us hat this mode of therapy might be useful in the man-gement of patients with complicated acute myocardial nfarction. If the frequency of infarct extension is as reat as recently suggested,[11] then it may be desirable o utilize therapeutic measures designed to protect schemic tissue for a more prolonged period of time.

Mechanism of beneficial effects of nitroglycerin: nalysis of the changes in our group of patients suggests hat nitroglycerin ointment exerts a favorable influence n myocardial oxygen consumption by virtue of the eductions in pulmonary capillary wedge pressure and ight atrial pressure, which are probably secondary to eripheral venous pooling. Additionally, the decrease n mean arterial pressure suggests a reduction in ven-ricular afterload. The reduction in heart rate-systolic lood pressure product further suggests a reduction in nyocardial oxygen consumption. Preservation of the ransmyocardial gradient despite the decrease in sys-emic pressure indicates that coronary perfusion pres-ure was maintained. The preservation of stroke index n the face of reductions in pulmonary capillary wedge nd mean arterial pressures indicates improved ven-ricular performance. Although this effect may have een mediated by a positive inotropic effect of nitro-lycerin, this possibility seems unlikely. Whatever the ause of the improved performance, the data suggest hat myocardial oxygen consumption was either di-inished or unchanged and that myocardial efficiency was therefore increased. Because the patients in our study had an average pulmonary capillary wedge pressure of 19 mm Hg, caution must be exercised in extrapolating these results to patients with normal or reduced left ventricular filling pressure. It is of note that the initial study in our Patient 4, who had a pulmonary capillary wedge pressure of 12 mm Hg, was terminated because of symptomatic hypotension.

Route of nitroglycerin administration: Although sublingually administered nitroglycerin has been used by some investigators, it produces a bolus effect and also has a short duration of action.[7,12] The problems of intravenous administration of nitroglycerin have previously been discussed. Nitroglycerin ointment applied topically provides a relatively safe and effective form of vasodilator therapy with a longer duration of action than that of other nitrate preparations. Furthermore, it permits retrieval of a portion of the dose should untoward side effects occur. The best mode of administration of nitroglycerin ointment remains speculative because the rate of absorption will be affected by the area of application, the cutaneous blood flow at the site of administration, the rate of evaporation and the dose. Without accompanying blood level measurements, proper evaluation of these factors is difficult. These measurements have been limited by technical problems involved in obtaining a reliable blood level estimate of the nitrates.

Clinical implication: Our study has demonstrated that nitroglycerin ointment applied in patients with acute myocardial infarction can produce significant improvement in left ventricular function and reduction in the determinants of myocardial oxygen consumption. Such use requires careful hemodynamic monitoring. The ultimate role of this type of therapy requires further study and, in particular, an evaluation of its effects on direct measurements of myocardial oxygen consumption, myocardial injury and prognosis.

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Medical Versus Surgical Treatment of Unstable Angina

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Unstable angina is an important symptom of coronary artery disease. Two general clinical presentations may occur: (1) stable angina with a recent increase in severity or angina of recent onset, or (2) acute coronary insufficiency or angina at rest with chest pain resembling that of acute infarction. The risk of death or infarction is greater in patients who have recurrent chest pain and ST-T wave abnormalities despite hospital treatment. In patients without electrocardiographic or serum enzyme evidence of a completed infarct, coronary arteriography and bypass graft surgery can be performed with an acceptably low mortality rate. Surgical treatment provides better symptomatic relief than medical management in many patients, but the significant incidence of perioperative infarction makes it difficult to determine if surgery prevents infarction. Some studies indicate that surgery improves survival in subgroups, but data from large scale randomized studies will be needed to answer this question securely. Patients with disease of the left main coronary artery should probably have surgical treatment.

Medical treatment will relieve symptoms in most patients with unstable angina and on a long-term basis may obviate the need for surgery. A preliminary period of intensive medical treatment before surgery may be advantageous since there is little evidence that survival rates are improved by treating unstable angina as an acute surgical emergency.

Operative treatment of unstable angina continues to be widely applied as evidenced by reports of the results of surgery from many medical centers. These contributions have clearly demonstrated that coronary arteriography and vein bypass surgery performed in patients with unstable angina have an acceptably low mortality rate and can provide substantial relief of symptoms. Although surgery may prevent late myocardial infarction, the incidence of perioperative infarction is sufficiently great to offset this advantage. Whether surgery improves survival rates can best be assessed with data from large scale randomized studies due during the next 5 years. In the meantime one must examine critical problems in the evaluation of treatment methods for unstable angina with particular reference to published data and the limits of present knowledge.

Definition of the Syndrome of Unstable Angina

Most workers agree that unstable angina consists of the following general clinical presentations:

Type I, angina pectoris: (1) Stable angina with a recent spontaneous increase in severity. (2) Angina of recent onset with progressive increase in severity.

Type II, angina at rest or acute coronary insufficiency: Patients in this category have recurrent episodes of prolonged pain at rest lasting at least 15 minutes. Their pain differs from that of ordinary angina b

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ts occurrence at rest, its longer duration, its poor relief with nitrates and its frequent association with other symptoms such as sweating, pallor, dyspnea or weakness. The pain may be relieved only by opiates. This presentation is the sole complaint in about 20 percent of patients with unstable angina. Type I angina may progress to type II angina at rest as the patient's symptoms become more severe.

In addition to the symptoms described, the classification of unstable angina requires the demonstration of objective evidence of coronary disease or myocardial ischemia and the exclusion of recent, completed myocardial infarction.

Objective Criteria of Coronary Disease

Three general objective criteria for the presence of coronary disease or ischemia may be used:

Electrocardiographic evidence of a prior healed myocardial infarct: This should not be an exclusive criterion. The object of treatment is to prevent infarction and preserve myocardial function; hence, it is equally important to identify the patient with unstable angina who has not had a prior infarct. About 20 to 60 percent of patients with unstable angina have electrocardiographic evidence of a prior infarct.[1–3]

Transient ST-T wave changes or cardiac arrhythmias during chest pain: Electrocardiographic findings consist of T wave inversion, S-T segment depression, S-T elevation and, occasionally, sinus bradycardia when inferior wall ischemia is present. Such changes usually occur during pain but may also be present in the absence of pain as revealed by continuous monitoring.[4] This is a reliable criterion of coronary disease but many patients with unstable angina may become pain-free soon after hospital admission and may not exhibit electrocardiographic changes.

Stress testing: In patients with unstable angina and normal electrocardiogram who do not exhibit chest pain or ST-T changes in the hospital, treadmill testing after 4 to 14 days of medical treatment may be useful in detecting myocardial ischemia. This method has limitations. The danger of stress testing during unstable angina has not been systematically evaluated. Patients with severe coronary disease may have a negative stress test.

Employment of these objective criteria will identify a group of patients with a high probability (approximately 95 percent) of having an abnormal coronary arteriogram.[5] If symptoms alone are used for selection, the incidence rate of abnormal coronary arteriograms may be lower because the study group may include patients with noncoronary pain simulating angina, such as patients with acute pericarditis, anxiety neurosis with hyperventilation or cardiomyopathy.[3]

Exclusion of Acute Completed Myocardial Infarction

This is an important criterion for the diagnosis of unstable angina because surgery in the presence of an acute infarct has a high operative mortality rate and has not been shown by acceptable studies to be beneficial. In addition, the medical treatment of unstable angina is different from that of recent myocardial infarction.

Serial electrocardiograms and serum enzyme determinations will usually be sufficient to exclude acute infarction but sources of error should be mentioned. Nontransmural, intramyocardial or subendocardial infarction may occur without the appearance of new Q waves. A new infarct in the area of a healed infarct may not be detected if Q waves of the prior infarct are present. Serial serum enzyme determinations will be helpful in patients with this condition, but if the infarction is "subacute" (progressing gradually over several days with slow release of enzymes), persistent diagnostic serum enzyme elevations may not occur. In addition, many patients with unstable angina, a normal electrocardiogram and only transient reversible electrocardiographic changes may exhibit transient elevation of serum enzymes to as much as twice the upper limit of normal without evidence of significant infarction. This observation was made several years ago by Resnick[6] and was recently confirmed by studies in the Palo Alto Veterans Administration Hospital.[1] Such enzyme elevations probably represent scattered areas of focal, intramural or subendocardial necrosis secondary to severe ischemia and their presence does not contraindicate surgical intervention.

Incidence of Unstable Angina

It is now generally accepted that a substantial number of patients with an acute myocardial infarction have premonitory symptoms for days or weeks preceding the infarction. Solomon et al.[7] reported that 65 percent of patients with acute infarction experienced suggestive premonitory symptoms 1 to 60 days before infarction. Chest pain compatible with angina or ischemia was noted in 90 percent of patients with prodromata. If such patients can be identified before the occurrence of an acute infarction and prompt surgical treatment is applied, it is logical to assume that infarction and death may be prevented. Because the study of Solomon et al. was a retrospective evaluation it is not known how many patients with similar symptoms did not have a myocardial infarct or die suddenly. Most of the patients in that study did not consider their symptoms sufficiently severe to consult a physician. For these reasons, the true incidence of unstable angina in our population is not clearly known.

Assessment of Mortality in Unstable Angina

The ability to identify patients with unstable angina who are at unusually high risk of death or infarction would be important. Several features of such patients have been described:

Electrocardiographic evidence of infarction or ischemia: Electrocardiographic evidence of prior infarction is not a significant risk factor in either unstable or stable angina.[8–10] Resting S-T segment depression or resting T wave abnormalities are associated with a poor prognosis in stable angina.[10]

Persistence of chest pain despite medical treatment in the hospital: Gazes et al.[8] and Krauss et al.[11] have shown that patients with persisting chest pain have

TABLE I

Clinical Features: Unstable Versus Stable Angina*

	Unstable Angina	Stable Angina
Patients (no.)	52	70
Mean age (yr)	53.0	52.2
Prior infarct (by ECG) (%)	34	60
Hypertension (history) (%)	32	31
Hypertension (DBP > 89 mm Hg) (%)	44	37
Serum cholesterol >249 mg/100 ml (%)	40	38
3 vessel disease (%)	53	69
1 vessel disease (%)	2	10
LV contraction abnormalities (%)	70	77

*Clinical preoperative characteristics of 52 patients treated surgically for unstable angina are compared with baseline data of 70 patients with stable angina treated medically. All patients in both groups had coronary arteriography and all were suitable for bypass graft surgery.

DBP = diastolic blood pressure; ECG = electrocardiogram; LV left ventricular.

TABLE II

Follow-up Data on 136 Patients Treated Medically for Stable or Unstable Angina

	Angina	
	Unstable	Stable
Patients (no.)	66	70
Mean age (yr)	52	52
Prior infarct (by ECG) (%)	56	60
Follow-up time (mo)	18	18
Total infarct (%)	15	7
Total mortality rate (cardiac) (%)	15	15.7
No angina (%)	9	20
Severe angina (%)	39	34
Late hospital entry (%)	39	17
Late operation (%)	10	11.4

ECG = electrocardiogram.

a substantially higher subsequent mortality rate than that of patients whose pain is promptly relieved by hospital treatment.

Features of electrocardiographic changes during pain: Patients with S-T segment elevation during pain do not appear to have different coronary arteriographic findings from those of patients who have other ST-T wave changes during pain. In addition, transient S-T segment elevation does not appear to carry a greater risk of death or infarction.[12]

Acute coronary insufficiency: It appears that patients presenting with acute coronary insufficiency (type II unstable angina) are at greater risk of infarction or death than those who present with angina alone (type I), but further studies are necessary to evaluate this finding.[13]

Ventricular arrhythmias: If continuous monitoring is used about 80 percent of patients with unstable angina are noted to have ventricular arrhythmias, consisting usually of ventricular premature beats. Patients with salvos of ventricular tachycardia, sustained ventricular tachycardia or ventricular fibrillation are probably at high risk but the incidence rate of such arrhythmias in unstable angina is not high (2 to 5 percent).

Other risk factors predicting poor survival: In studies of stable angina[9] the number of arteries involved, hypertension, congestive heart failure, abnormal hemodynamics and left ventricular asynergy were associated with poor survival in medically treated patients. Other studies[14] have shown that cardiac enlargement is a major risk factor. The variables are probably also important predictive factors in unstable angina.

Noninvasive methods of assessment: Assessment of risk in unstable angina using noninvasive methods would permit more precise selection of patients for coronary arteriography and surgery. Heart size is an important factor in assessing survival in stable angina; therefore, it is important to refine present noninvasive methods of evaluating heart size and ventricular volume with roentgenographic methods (heart volume), echocardiography (hypertrophy-diastolic dimensions-left atrial size) and isotope angiography (ventricular volume, ejection fraction, aneurysm). Data from large scale randomized studies will provide further information on identifying patients at great risk.[14]

Does unstable angina differ from stable angina in terms of prognosis? Most studies have indicated that unstable angina is associated with a greater risk of infarction and death than stable angina but the difference is not striking. In the Myocardial Infarction Research Unit (MIRU) study of unstable angina, medically treated patients had a mortality rate of 7.7 percent at 1 year.[15] In the Veterans Administration Cooperative Study the overall mortality of medically treated patients with stable angina was 8 percent at 1 year.[14] At the Palo Alto Veterans Administration Hospital data in 66 patients with unstable angina and 70 patients with stable angina were compared after 1 year of medical treatment.[1] Table I indicates that both groups were similar in regard to several clinical descriptors. Table II indicates that the principal difference between the two groups was a higher incidence rate of nonfatal infarcts in the group with unstable angina (24 percent versus 7 percent). There was no difference in mortality. Similar data are available from the MIRU study where the incidence of nonfatal myocardial infarcts in patients with unstable angina was 15 percent in 7 months.

Why do many reports of the prognosis of medically treated unstable angina indicate a higher 1 year mortality rate than was observed in the MIRU study or the Palo Alto Veterans Administration Study? Differences in patient population and selection, diagnostic criteria, time of death and follow-up evaluation are important factors. All patients in the MIRU and Palo Alto studies were selected by the carefully defined diagnostic criteria outlined in this review. Patients who were not suitable for surgical intervention were excluded as were those who died in the first 4 days after hospital admission.

Evaluation of Risk by Angiography

Coronary arteriography and left ventricular angiography provide the most important information re-

garding prognosis in medically treated patients with stable angina. Important factors are: (1) number of diseased coronary vessels, (2) presence of left main coronary lesions, (3) contraction abnormalities, (4) ejection fraction, and (5) left ventricular end-diastolic pressure. Angiographic features associated with a poor prognosis in stable angina are likely to be associated with a poor prognosis in unstable angina, but it is not practical to perform angiography in all patients with unstable angina. For this reason, noninvasive methods of identifying patients at high risk who should be studied by arteriography will continue to be important.

Risk of coronary arteriography and surgery: Earlier studies reported substantially higher mortality rates for arteriography and surgery in patients with unstable angina. The risk of death has now been substantially reduced and appears to be no greater than that of patients with stable angina. At the Palo Alto Veterans Administration Hospital, 74 patients with unstable angina underwent arteriography with no mortality and one nonfatal infarct.[1] Among 60 patients who underwent bypass graft surgery, there were two operative deaths (3.3 percent). Death occurring within 24 hours of arteriography or 30 days of surgery should be classified as a complication of these procedures.

Perioperative Myocardial Infarction

Incidence: The incidence of perioperative infarction is similar in patients with stable and unstable angina. In the MIRU study perioperative infarction occurred in 9 of 65 (14 percent) of patients[15]; in the Palo Alto Veterans Administration study it occurred in 15 percent of 52 patients with unstable angina and in 14 percent of 113 patients with stable angina. A similar incidence of perioperative infarction in patients with unstable angina has been reported by others.[2,3,16,17]

Because a principal reason for surgical intervention is the prevention of infarction, it is disturbing that surgery is so frequently accompanied by infarction. Perioperative infarction results in a 1 year incidence rate of infarction that is higher or equal to the incidence rate in medically treated patients. In the MIRU study the surgical group (65 patients) had a total of 9 infarcts in 7 months (14 percent), of which 9 were perioperative; the medical group (73 patients) had 11 infarcts (15 percent). In the Palo Alto Veterans Administration study there were 8 infarcts (all perioperative) in 52 surgical patients (15 percent) compared with 10 infarcts in the 66 medical patients (15 percent). Longer follow-up studies are needed to determine if the incidence of late infarction is smaller in surgically than in medically treated patients.

Clinical significance: It might be argued that perioperative infarction is more benign than the usual clinical infarction and therefore, should not be included in follow-up statistics. However, several features of perioperative infarction indicate that this is not a benign complication f surgery:

1. Perioperative infarction is an important cause of operative death, and analysis of deaths after coronary surgery indicate that evidence of recent infarction is present in about 75 percent of cases.[16,17] Assad-Morell et al.[18] reported that perioperative infarction was the cause of 10 of 16 operative deaths in a consecutive series of 500 vein bypass graft operations. Thus, if the incidence of perioperative infarction in a given surgical center is 12 percent and the operative mortality rate is 6 percent and if half of the deaths are due to operative infarction, then the mortality rate of perioperative infarction in that hospital is 25 percent.

2. Perioperative infarction is associated with late left ventricular contraction abnormalities that are similar to those observed in nonoperative infarction.[19]

3. The incidence of perioperative infarction is probably greater than is usually reported: Most reports use electrocardiographic evidence of new Q waves or QRS abnormalities as evidence of perioperative infarction. Such criteria detect only transmural infarcts. If one uses the criteria of persisting ST-T abnormalities plus serum enzyme abnormalities to detect nontransmural infarction the incidence of perioperative infarction will be greater.[20]

Is Unstable Angina an Acute Surgical Emergency?

Several workers consider unstable angina an acute emergency requiring prompt arteriography and surgical intervention to obtain an optimal therapeutic result. There are no convincing data to support this view. It might be expected that some patients will die within 2 to 4 days of hospital entry and that early surgery will prevent death or infarction. Studies of unstable angina reveal a small number of early hospital deaths and infarction. In the study of Gazes et al.,[8] 2 of 54 patients at high risk died within 72 hours after admission. In the MIRU study 2 of 73 medically treated patients died in the hospital.[15] In the Palo Alto Veterans Administration study 1 of 66 patients died within 4 days of admission.[1] Other workers[11] have reported similar data. An important hazard of prompt arteriography and surgical intervention is the possibility of operating on patients in the early stage of transmural myocardial infarction. In such patients the operative mortality is great and there is no evidence that the amount of infarcted myocardium is decreased by surgery.[21] Thus, the possible small advantage gained by early surgery may be offset by the greater risk associated with surgery in patients with undetected early infarction. It is possible that surgical intervention may be more effective and associated with a smaller incidence of perioperative infarction if it is preceded by a period of medical treatment for 1 to 4 weeks, especially if intensive medical therapy is used.[22,23] Unfortunately, results of systematic studies of delayed semi-elective surgery in unstable angina have not been reported and this procedure is not being evaluated in current protocols.

Evaluation of Surgical Versus Medical Treatment of Unstable Angina

From an analysis of available reports and on the basis of experience with large scale prospective studies several problems are evident in data collection and evaluation of surgical versus medical management of unstable angina.

1. The clinical syndrome must be clearly defined, and objective methods of confirming the presence of myocardial ischemia must be used.
2. Acute completed myocardial infarction must be excluded by appropriate methods.
3. Subgroups of patients who might be expected to be at great or small risk of death or infarction should be defined.
4. A 2 to 4 day observation period in the coronary care unit is necessary to confirm the diagnosis, exclude infarction, obtain the patient's cooperation and informed consent and arrange for coronary arteriography and surgery.
5. *For accurate data analysis* the starting time for observations of mortality and morbidity should be predetermined and should be the same for surgical and medical treatment groups if a comparative study is being carried out. Several studies have used a starting time of 4 to 5 days after hospital entry. Unless this is done a statistical bias in favor of surgery may occur. For example, if a patient dies 3 days after entry to the coronary care unit while receiving medical therapy, this death should not be included in the study statistics since the patient died before arteriography and surgery could have been performed.
6. It is highly desirable to perform coronary arteriography and left ventricular angiography in all patients even if all patients are not going to receive surgical treatment. Coronary arteriography and angiography are the most reliable methods of assessing prognosis and, without this information, one cannot be certain that both groups are similar.
7. *Left main coronary arterial stenosis* is now recognized as a serious lesion with a poor prognosis and one in which surgical management is preferable to medical treatment.[24] In unstable angina 8 to 12 percent of patients will have left main coronary lesions. These observations provide a justification for coronary arteriography in all patients with unstable angina in any comparative study and a justification for surgery in patients with such lesions.
8. *Treatment failures:* Patients with unstable angina receiving optimal medical treatment may have progression of their symptoms. There is increasing evidence that surgical treatment in both stable and unstable angina relieves symptoms more effectively than medical treatment alone. Thus the physician faces an ethical problem: At what point should one abandon medical treatment and advise surgical intervention? In comparative studies treatment failures should be carefully defined so that a systematic policy is followed.

Evaluation of Results of Treatment Methods

In addition to assessing the objective end points of cardiac death and nonfatal infarction, one must evaluate the "quality of life" since most studies indicate that this aspect of unstable angina is improved more effectively by surgical than by medical treatment. General assessment by the patient as to whether angina is decreased, unchanged or worse is difficult to evaluate because of the placebo effect of surgery. The New York Heart Association functional classification is not suitable for the evaluation of angina. A simple questionnaire or assessment form has been developed for evaluating stable angina and has been modified for patients with unstable angina.[25] The following factors are evaluated:

1. Severity or frequency of symptoms and amount of effort required to produce symptoms.
2. Amount of medication taken daily to relieve angina including nitrates and propanolol.
3. General level of daily physical activity (sedentary, light, moderate or heavy work).

Factors 1 and 2 clearly affect the severity and frequency of anginal attacks. Since many patients with unstable angina may have minimal angina on effort but may experience repeated attacks of severe angina or acute coronary insufficiency requiring hospital admission, hospital entry for chest pain is a reasonable criterion of recurrent symptoms. Objective methods of evaluating myocardial ischemia such as treadmill testing are properly not used in unstable angina, but pacing stress during angiography would be an acceptable substitute. An increase in left ventricular end-diastolic pressure during stress or pacing appears to be a more sensitive measure of myocardial ischemia for repeat studies than the resting ejection fraction.[26]

In follow-up studies one must determine if patients lost to follow-up are alive or dead. This is an important problem since in a hypothetical study of 100 patients with a mortality rate of 8 percent, 8 more deaths would double the rate to 16 percent. Such a study may still have a 92 percent follow-up success rate if all the patients lost to follow-up were lost because of death.

Sample Size and Duration of Follow-Up

Because the incidence of myocardial infarction related to surgery appears to distort the incidence of infarction during the first year of follow-up study of surgically treated patients a follow-up period of 3 to 5 years is needed to determine if surgery can prevent late infarction. Studies in stable angina have indicated that in both medically and surgically treated patients the highest death rate occurs during the first year and the same is probably true for the incidence of nonfatal infarction. For this reason a follow-up period of more than 5 years may result in diminishing returns in terms of statistically valid differences.

If the expected mortality rate was 20 percent during the first year and 10 percent annually thereafter and if one mode of therapy successfully reduced the mortality rate by half, approximately 300 patients would be required in each treatment group to achieve a statistically significant difference at 5 years. If one wishes to examine differences in subgroups such as patients with single vessel disease, the initial sample size must be increased so that an adequate number of patients in each subgroup will be included for analysis. The Veterans Administration Cooperative Study plans to enter a total of 750 patients with a 5 year follow-up period in its projected evaluation of surgical versus medical treatment of unstable angina.

This is the critical problem with small studies; that is, the sample size and the follow-up period are not sufficient to demonstrate statistically significant differences. For this reason large scale cooperative studies will be necessary to answer most of the critical questions regarding treatment of unstable angina.

Randomization

Prospective randomization of patients to different treatment modes is an effective method of ensuring that each treatment group is composed of similar patients. It is an ethically acceptable method provided that guidelines for fully informed consent are followed. It has been successfully employed in the Veterans Administration Cooperative Study of Stable Angina.

Randomization may be impractical in a hospital setting where several physicians influence the decision to enter the patient into a randomized study. For example, some physicians may be willing to randomize only younger patients at low risk. If this is a general tendency, the study group will not contain a representative cross section of patients with the disease being evaluated. Randomized studies are most successful when nearly all eligible patients are entered into the study and the reasons for not entering patients are clearly stated in a screening log. In the Veterans Administration Cooperative Study of Stable Angina, a screening log is maintained by each participating hospital. The names of all eligible patients are entered into the log and specific reasons are listed for failure of any patient to enter the study.[14]

If randomization is not feasible, data banking is a substitute method of analysis. Many patients with unstable angina may elect not to have surgical therapy for personal or logistic reasons or upon the advice of their physician. If coronary arteriography has been performed, one can determine whether the condition of such patients is operable. These patients are then acceptable control subjects for comparison with similar patients who receive surgical therapy. Several investigators[1,27–29] have successfully used this method with results that are very similar to those obtained from a randomized study.

Present Status of Controlled Studies

This review will not evaluate in detail reports of comparative studies of medical versus surgical treatment of unstable angina. A summary evaluation of five studies reveals the following data: In 280 patients treated medically with a mean follow-up time of 18 months the mortality rate was 13.8 percent and the incidence rate of nonfatal myocardial infarction 12 percent. In 334 patients treated surgically with a similar mean follow-up time the mortality rate was 7.1 percent and the incidence rate of nonfatal infarction 18.2 percent. Most of the infarcts in the surgical group were perioperative.[1,5,15,29–34]

Further data will be needed from large scale studies to evaluate the comparative mortality and morbidity in identifiable subgroups in which the risk of medical treatment alone may be greater than that of surgical treatment.

Medical Treatment

Most patients with unstable angina become symptom-free with appropriate medical management.[23] The major objective of treatment is to achieve a decrease in cardiac work to relieve symptoms, reduce ischemia, prevent infarction or arrhythmic death and relieve coronary spasm, which may be present in some patients. Bed rest, sedation, reassurance and relief of pain with meperidine or morphine are important measures that are often overlooked in modern, busy coronary care units. Sedation with phenobarbital or diazepam may be used for the first 2 or 3 days. Barbiturates should be used if necessary to ensure restful sleep.

Patients with unstable angina are fearful of the possibility of sudden death or infarction and are apprehensive about diagnostic or therapeutic procedures that may be dangerous or painful. Invasive procedures such as central venous catheters, Swan-Ganz studies or arterial punctures should be employed only when necessary to obtain important data that may significantly influence therapy. An organized program of patient education should be started as soon as possible. This should include participation by the coronary care unit nursing staff and the attending physicians. The essential features of the patient's disease should be explained in lay terms, and the nature and purpose of all diagnostic and therapeutic procedures should be described. Adequate time should be allowed for complete and thorough answers to any questions by the patient or concerned relatives. Some hospitals provide appropriate written material in lay language that is suitable for the intelligent motivated patient. These measures may be more effective in reducing cardiac work and arrhythmogenicity than pharmacologic interventions.

Nitrates provide the most effective, flexible means of relief of angina and ischemia. Nitroglycerin should be available at the bedside for prompt use when anginal pain begins. Patients should be instructed in the proper use of nitroglycerin. The hemodynamic effect is greater when the patient sits on the edge of the bed, which enhances pooling. Nocturnal dyspnea may be promptly relieved with nitroglycerin and erect sitting. The patient should be told that a slight headache or throbbing sensation in the head or neck is a useful sign that the nitroglycerin is effective. If unpleasant headache is produced the dose should be decreased and, if necessary, aspirin or empirin compound may be used.

Longer-acting nitrates, such as isosorbide dinitrate given 4 to 6 times daily, will provide a more sustained effect upon the circulation for periods of up to 4 hours.[35] Sublingual tablets should be employed.

For recurrent angina and nocturnal angina nitroglycerin ointment will provide a more persistent hemodynamic and symptomatic effect.[36]

Propranolol should be employed with nitrates because its negative inotropic and chronotropic effects reduce cardiac work because it inhibits the increased heart rate produced by nitrates. A dose of at least 80 mg daily is required for a demonstrable circulatory response and the usual daily dose is 160 mg. Propranolol should be given before meals and longer-acting nitrates after meals so that the slower circulatory effect of propranolol will more effectively inhibit the increase in heart rate produced by the shorter acting nitrates. Resting heart rate should be maintained between 60 and 70 beats/min by adjusting the dose. Effective slowing of the heart rate

can be achieved in most patients with unstable angina. Of 100 such patients observed at the Palo Alto Veterans Administration Hospital 30 percent had a resting heart rate exceeding 80 beats/min on entry to the coronary care unit.

Nitrates and propranolol should be administered even in the absence of recurrent pain or signs of myocardial ischemia because prevention is as important as therapy. Many patients have myocardial ischemia or ischemic left ventricular dysfunction without chest pain.[4] This management regimen should be continued for at least 7 to 14 days. The regimen should be continued on a long-term basis in patients with stable angina. The effectiveness of propranolol in the relief of myocardial ischemia and the prevention of infarction is well illustrated by the untoward effects of the sudden cessation of the drug in patients with stable angina.[37]

Pulmonary congestion with dyspnea, orthopnea, rales and gallop rhythm is not an absolute contraindication to the use of propranolol in patients with recurrent chest pain since it may have an ischemic origin. In such patients the administration of digitalis preparations, and a diuretic drug with modest sodium restriction, is indicated, and administration of propranolol and nitrates may be continued. If prompt improvement does not occur with this combination of drugs, the use of propranolol should be discontinued.

If pulmonary edema is present with a reduction in arterial partial pressure of oxygen (PO_2) administration of oxygen at low flow rates with use of a light plastic face mask is indicated. Hypoxia increases heart rate and catecholamine release and this can be minimized by administration of oxygen. Oxygen also slows the heart rate by a more direct cardiac effect.[38]

Nitroprusside infusion may be useful in unstable angina under some circumstances including the following: (1) persisting pain either not relieved by nitrates or occurring in patients who cannot tolerate nitrates; (2) left ventricular failure not responding to usual therapeutic measures; and (3) persisting hypertension with recurrent chest pain not relieved by usual measures.

Hypertension is frequently observed in patients with unstable angina. In the Palo Alto study 34 percent of 100 patients with unstable angina had a history of prior hypertension and 22 percent had a diastolic pressure exceeding 89 mm Hg on entry to the coronary care unit. Episodes of angina may be accompanied by an acute increase in systemic pressure. Hypertension greatly increases cardiac work and myocardial oxygen consumption.[39] The maintenance of a low blood pressure is an important objective of treatment of unstable angina. If this cannot be achieved by rest, sedation, nitrates or propranolol, a diuretic drug and methyldopa may be administered orally. Intravenous administration of methyldopa or nitroprusside may be used if significant hypertension persists despite these therapeutic measures.

Serious cardiac arrhythmias, especially ventricular tachycardia and fibrillation, may occasionally occur in unstable angina, and appropriate suppressive pharmacologic therapy and direct current cardioversion should be used when indicated.

Approximately 5 to 15 percent of patients with unstable angina will have clear evidence of myocardial infarction during their hospital course. Subendocardial infarction will be evident when persistent high levels of serum enzymes occur in the presence of prolonged S-T segment depression and T wave inversion. Transmural infarction will be evident from the appearance of new Q waves or other QRS abnormalities. Conventional management of acute infarction is indicated in such patients.

The role of anticoagulant agents in managing unstable angina remains in doubt because of the lack of appropriately controlled prospective studies. If anticoagulant therapy is employed heparin, administered intravenously, should be selected initially because of its rapid action. Orally administered anticoagulant drugs require several days to obtain a maximal effect on clotting factors. The role of aspirin is currently being investigated by a Veterans Administration Cooperative study.

All patients with unstable angina should receive careful systematic medical treatment, and this regimen should include patients who are being considered for surgical management.

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The Heart in the Hurler Syndrome

Gross, Histologic and Ultrastructural Observations in Five Necropsy Cases

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Clinical and morphologic features of the cardiovascular system are described in five necropsy patients with the Hurler syndrome. In all five patients the coronary arteries, four cardiac valves, mural endocardium of all four chambers, myocardial walls and aorta were affected in a characteristic manner. All of these sites contained large clear cells known as Hurler cells (readily visible by light microscopy). In addition, granular cells were observed in semi-thin (1 μ) sections and by electron microscopy in the coronary arteries, atrioventricular (A-V) valves and in myocardial interstitium. These latter cells appear to produce collagen in an abnormal way and are probably responsible for the heavy deposits of collagen in the cardiovascular system of patients with the Hurler syndrome. In the cardiac muscle cells, in smooth muscle cells of the coronary arteries and in fibroblasts, wherever located, deposits of acid mucopolysaccharides and glycolipids usually were also observed. The acid mucopolysaccharide deposits were observed easily with light microscopy except in the cardiac muscle cells where they were seen only with electron microscopy. The glycolipid deposits, observed only on examination of 1 μ thick sections or with electron microscopy, have not previously been observed in coronary arteries or in myocardial cells.

The infiltration into the heart by these cells and deposits in all five patients resulted in severe narrowing of the extramural coronary arteries, considerable thickening of the cardiac valves (the left-sided more than the right-sided valves), generalized thickening of mural endocardium and "stiffening" of the myocardial walls. Thus, the cardiovascular lesions in the Hurler syndrome are specific and life-threatening.

The mucopolysaccharidoses are a heterogeneous group of inherited metabolic diseases that have been subdivided into several well defined syndromes on the basis of their clinical, genetic and biochemical features.[1] Patients with the Hurler syndrome are characterized by dwarfism, severe mental retardation, skeletal malformations, hepatosplenomegaly, corneal opacities and various cardiovascular lesions.[2] These patients demonstrate intracellular accumulation of acid mucopolysaccharides and glycolipids in various tissues[3–11] and excessive urinary excretion of dermatan and heparin sulfates.[12] The Hurler syndrome is due to genetic deficiency of specific lysosomal hydrolases that normally are responsible for degradation of acid mucopolysaccharides.[13,14] Two enzymatic abnormalities of pathogenetic importance have been found in the Hurler syndrome: the first concerns the concentration of alpha-L-iduronidase which is consistently reduced in cultured Hurler fibroblasts,[15–17] and the second, the concentrations of isozymes B and C of beta-galactosidase which have variously been reported to be normal or decreased in different tissues.[18–21] The accumulation of excessive amounts of acid mucopolysaccharides in cultured Hurler fibroblasts is due to deficiency of a specific protein "Hurler corrective factor" required for degradation of these

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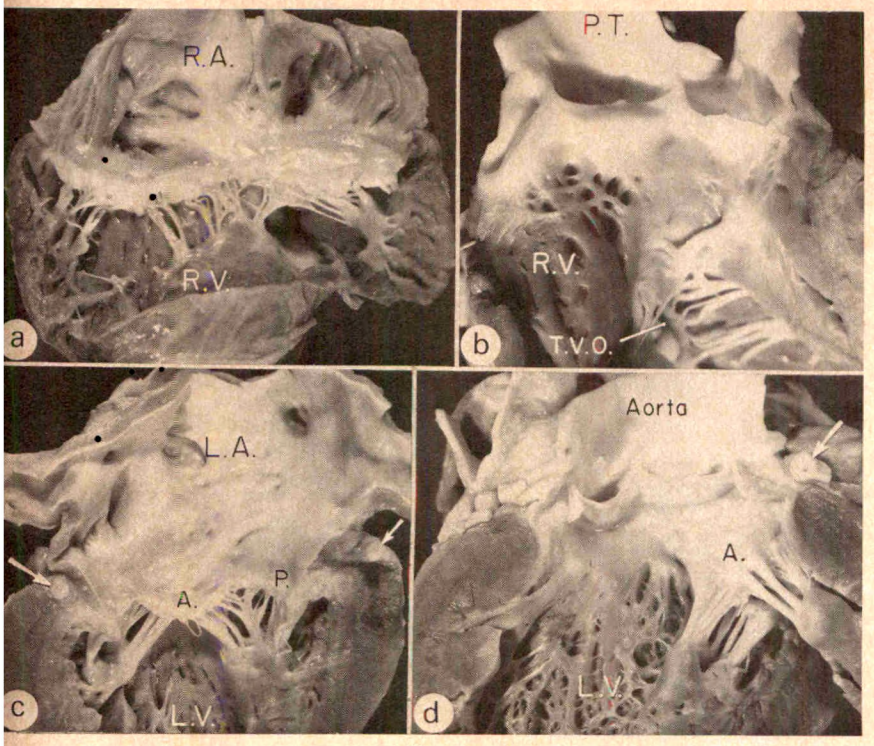


FIGURE 1. Case 2. Opened right (**a** and **b**) and left (**c** and **d**) sides of the heart of a 10 year old boy with typical features of the Hurler syndrome. All four cardiac valves and the mural endocardium of all four cardiac chambers were diffusely thickened. **a,** opened right atrium (R.A.), tricuspid valve and right ventricle (R.V.). **b,** opened pulmonary trunk (P.T.) pulmonic valve and right ventricular (R.V.) outflow tract. T.V.O. = tricuspid valve orifice. **c,** opened left atrium (L.A.), mitral valve and left ventricle (L.V.). The **arrows** show a severely narrowed left circumflex coronary artery. A = anterior, P = posterior mitral leaflets. **d,** opened left ventricle (L.V.), aortic valve and aorta showing thickening of both valves and the mural endocardium. The **arrow** again shows severe narrowing of the left coronary artery. A = anterior mitral leaflet.

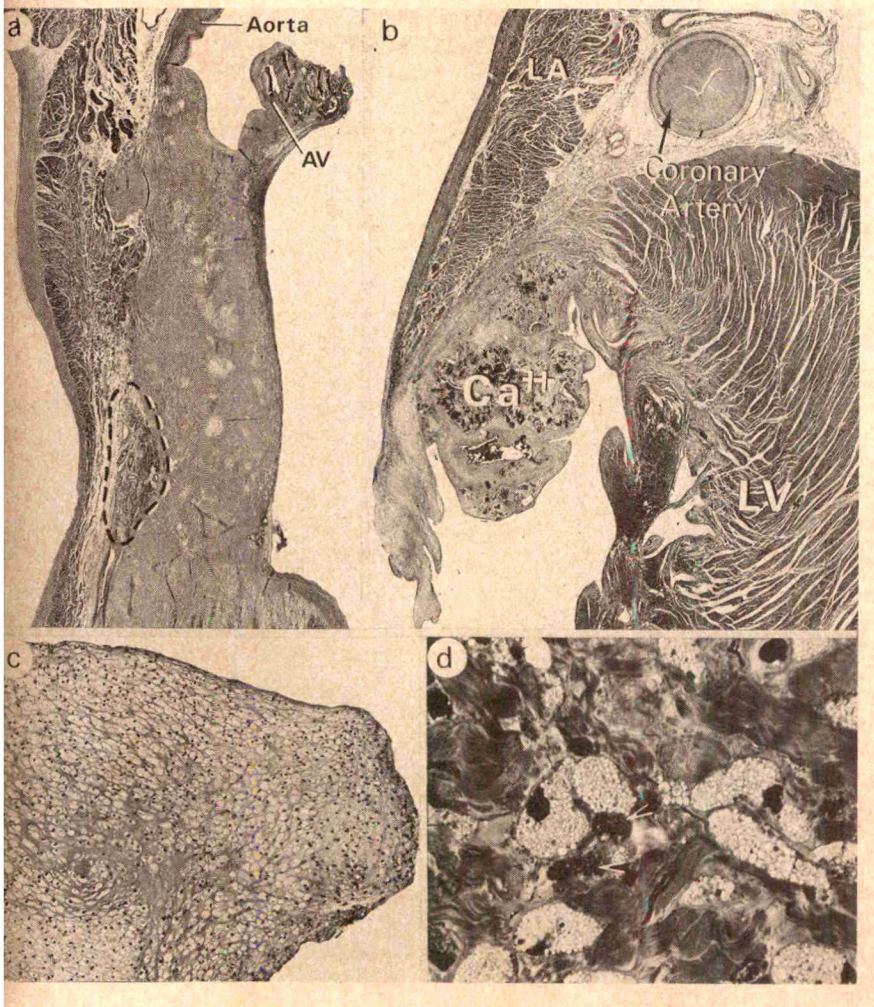


FIGURE 2. Case 1. Aortic and mitral valves. **a,** longitudinal section of the right anterior aortic valve (AV) cusp and a portion of the junction between membranous ventricular septum and posteromedial commissure of the mitral valve. The penetrating portion of the atrioventricular bundle is enclosed by the dashed lines. The pale areas represent clusters of clear cells. Calcific deposits are present in the aortic valve cusp. **b,** longitudinal section through posterior mitral leaflet, left atrium (LA) and left ventricle (LV). A large deposit of calcium Ca++) is present in the mitral anular area. The narrowed left circumflex coronary artery is designated by the **arrow. c,** tip of mitral valve leaflet showing large numbers of clear cells and patches of hyalinized collagen. **d,** section of glutaraldehyde- and osmium-fixed, plastic-embedded mitral valve showing clear cells, granular cells **(arrowheads)** and bundles of dense collagen. Hematoxylin-eosin stain (**a** and **c**), Movat stain (**b**) and toluidine blue stain (**d**): ×5 (**a**), ×6 (**b**), ×100 (**c**), ×400 (**d**). (Reduced by 35 percent.)

compounds,[22,23] and this corrective factor has been shown to be alpha-L-iduronidase.[17]

Morphologic findings in the Hurler syndrome were first described by Tuthill[24] in 1934. Subsequent morphologic studies have shown that the most characteristic light microscopic finding is the presence of cells containing large amounts of storage material in many of the affected organs.[25–28] These cells are frequently called "gargoyle cells," "balloon cells" or "clear cells" as a result of the vacuolization produced by the extraction of the storage materials during histologic processing, because of their solubility in ordinary fixatives. After appropriate fixation procedures, most of these cells give positive histochemical staining reactions for acid mucopolysaccharides.[9,10,29,30] Electron microscopic studies of different tissues from patients with the Hurler syndrome, including liver, central and peripheral nervous system, eye, skin, cartilage, peripheral blood lymphocytes and hypophysis, have revealed large membrane-bound cytoplasmic vacuoles that are believed to contain acid mucopolysaccharides and glycolipids.[10,11,30–39] These structures also have been shown to contain acid hydrolases, thus demonstrating their lysosomal nature.[30,35,37]

Despite the occurrence of cardiovascular lesions in patients with the Hurler syndrome, relatively few investigations of the heart and blood vessels in this syndrome have been reported,[10,30,40–43] and all but two[10,30] of these were light microscopic studies only. Except for the studies of Lagunoff et al.[10,30] on the fine structure of the mitral valve, no information is available concerning the ultrastructural aspects of the cardiovascular lesions in the Hurler syndrome. This study presents gross, histologic, histochemical and ultrastructural observations on the cardiovascular system in five necropsy cases of the Hurler syndrome.

Patients Studied

Detailed morphologic studies were made of tissues obtained at necropsy from five children (one girl and four boys), including two brothers (Patients 2 and 3), with typical clinical, chemical and morphologic features of the Hurler syndrome. Each had moderate dwarfism, corneal opacities, grotesque facial appearance, protuberant abdomen, inguinal hernias, typical deformities in the limbs and mental retardation. Urinary excretion of dermatan sulfate and heparitin sulfate was increased in each patient. None of the five patients had symptoms of cardiac dysfunction; however two patients (Cases 1 and 3) had systolic murmurs (grade 2/6 intensity), loudest at the apex; three (Cases 1, 2 and 5) had mild cardiomegaly by chest roentgenogram; two (Patient 3, who had right atrial hypertrophy and right axis deviation, and Patient 5, who had low voltage) had abnormal electrocardiograms and two (Cases 3 and 4) had systemic hypertension. One patient (Case 2) had

TABLE I

Cardiac Gross and Histologic Findings in Five Patients With the Hurler Syndrome

	Patient no.				
	1	2	3	4	5
Age (yr) at death	6	9	11	7	16
Gross findings					
Cardiac weight (actual) (g)	95	110	150	130	150
Cardiac weight (expected) (g)	94	115	122	100	240
LV wall thickness (mm)	10	13	11	14	12
RV wall thickness (mm)	5	2	3	5	3
Histologic findings*					
Valves					
Clear cells	+++	+++	+++	+++	+++
Granular cells	+	+	+	+	+
Inflammatory cells	+	+	+	+	+
Fibrosis	++	++	++	++	+++
Collagen degeneration	++	++	+	+	++
Calcification	0	+	+	0	+
Vascularization	0	+	+	+	+
Mural endocardium					
Clear cells	+	+	+	+	+
Inflammatory cells	+	+	+	+	+
Fibroelastosis	+	+	+	+	+
Myocardium					
Clear cells	+	+	+	+	+
Granular cells	+	+	+	+	+
Inflammatory cells	+	0	+	+	+
Fibrosis	+	+	+	+	+
Necrosis	0	0	++	0	0
Epicardium					
Clear cells	0	0	+	0	+
Inflammatory cells	0	+	+	+	+
Fibrosis	0	+	+	0	0
Nerve fibers					
Clear cells	+	+	+	+	+

*Severity of changes rated as + = mild; ++ = moderate; +++ = severe and 0 = absent.
LV = left ventricle; RV = right ventricle.

TABLE II

Histologic Features of Coronary Arteries and Aorta in Five Patients With the Hurler Syndrome*

	Patient no.				
	1	2	3	4	5
Coronary arteries					
Extramural					
Intima					
Clear cells	+++	+++	+++	+++	+++
Granular cells	+	+	+	+	+
Fibrosis	++	++	++	++	++
Media					
Clear cells	+	+	+	+	+
Granular cells	0	0	0	0	0
Luminal narrowing (%)					
Left main	51–75	51–75	>75	51–75	51–75
Left anterior descending	>75	>75	>75	>75	>75
Left circumflex	51–75	51–75	51–75	<50	<50
Right	>75	>75	>75	<50	51–75
Intramural					
Intima					
Clear cells	+	+	+	+	+
Granular cells	0	0	0	0	0
Luminal narrowing	0	0	0	0	0
Media					
Clear cells	0	0	0	0	0
Granular cells	0	0	0	0	0
Aorta					
Intima					
Clear cells	+	+	+	+	+
Granular cells	0	0	0	0	0
Atherosclerosis	+	+	+	+	+
Media					
Clear cells	+	+	+	+	+
Fragmented elastic fibers	+	+	+	+	+

*Severity of changes rated as + = mild; ++ = moderate; +++ = severe and 0 = absent.

ascites and severe subcutaneous edema, probably the result of portal hypertension. The ages of these patients at the time of death ranged from 6 to 16 years. None of the patients died of cardiac causes.

Gross Anatomic and Histologic Findings

Gross Findings

At necropsy, structural alterations characteristic of the Hurler syndrome were present in the liver, spleen, lymph nodes, bone and nervous tissue. Heart weight was normal in three patients and increased in two (Cases 3 and 4). The subepicardial adipose tissue was practically absent, and the coronary arteries were rigid and thickened. In all five patients, the mural endocardium in all four chambers was diffusely thickened, but to a greater extent on the left than on the right side of the heart. No thrombi were present in any of the four cardiac chambers in any of the five patients. The leaflets of all four cardiac valves were diffusely thickened in all five patients. The thickening was most pronounced at the free margins, which had an irregular nodular appearance (Fig. 1). This appearance was most striking in the mitral valve. The left-sided cardiac valves in all five patients were considerably more thickened than were the corresponding right-sided valves. The mitral valve in all five patients was thicker than any of the other three valves. The chordae tendineae of the atrioventricular (A-V) valves were moderately thickened and shortened (Fig. 1, a and c). The commissures were not fused and none of the valve orifices appeared either stenotic or incompetent. Three patients (Cases 2, 3 and 5) had calcific deposits in the angle just beneath the basal attachment of the posterior mitral leaflet (so-called mitral anular calcification) as well as smaller calcific deposits on the anterior mitral leaflet and on the aortic aspect of the aortic valve cusps (Fig. 2, a and b). The tricuspid and pulmonary valves were free of calcific deposits. Serial sectioning of each of the four major extramural coronary arteries in each patient (sections were made 0.5 cm apart) disclosed diffuse thickening of the arterial walls, causing severe (greater than 75 percent) luminal narrowing at many sites (Fig. 1, c and d). Thrombi were not observed in any of the arteries.

Histologic Findings

Histologic studies (Tables I and II) disclosed that the valve thickening was due mainly to the presence of large cells with clear cytoplasm (gargoyle, Hurler, clear or balloon cells) and of bundles of collagenous tissue with variable degrees of hyalinization (Fig. 2, c and d). Few mononuclear cells were present in the subendocardial areas of all valves, and small vascular channels were observed in the valve leaflets of all five patients. Increased amounts of collagen and numerous clear cells were responsible for the thickening of the chordae ten-



FIGURE 3. Case 2. Atrioventricular (A-V) bundle. **a** and **b,** longitudinal sections, one (**a**) stained by hematoxylin-eosin and the second (**b**) by Alcian blue, through the region of the A-V bundle (enclosed by **dashed lines**). Large amounts of acid mucopolysaccharide material **(dark)** is present in the region of the central fibrous body and in the tricuspid valve (TV) leaflet. AS = atrial septum; VS = ventricular septum. **c,** A-V bundle cells interspersed with clear cells and granular cells. **d,** small artery in the area of the A-V bundle. Its wall is infiltrated by clear cells. Periodic-acid Schiff stain (**c**) and hematoxylin-eosin stain (**d**): ×4 (**a** and **b**), ×400 (**c**), ×250 (**d**). (Reduced by 27 percent.)

dineae, the membranous portion of the ventricular septum and the anuli of the A-V valves. The thickening of the mural endocardium resulted primarily from proliferation of elastic and collagenous fibrils, but a few clear cells also were present.

Small foci of myocardial fibrosis and clear cells were present in the basal third of the left ventricular walls in all five patients. Foci of fibrosis were most prominent in the left ventricular papillary muscles of Patients 2 and 3. Patient 3 had foci of myocardial necrosis in the subendocardial region of the left ventricular posterior wall and in the posteromedial papillary muscle. In the one patient (Case 2) in whom sections of the A-V node were examined, focal accumulations of clear cells were present between the A-V nodal cells and in the muscular layer of the A-V nodal artery (Fig. 3, a to d).

The severe luminal narrowing of the coronary arteries was caused primarily by thickening of the intima, which contained numerous typical clear cells and increased amounts of collagen bundles (Fig. 4, a to d). Clear cells also were present in the medial layers of these vessels and in some of the intramural coronary arteries in all five patients.

In the aorta, multiple yellow and fibrous atherosclerotic plaques were present in all five patients (Fig. 5, a and b). Likewise, the aortic intima contained clear cells (Fig. 5c). Small numbers of mononuclear inflammatory cells, calcific deposits and extracellular cholesterol clefts also were present in the aortic intima of Patients 3 and 5. Similar infiltration by clear cells was observed in the intima of the carotid arteries and of branches of the renal and hepatic arteries (Fig. 5d); however, significant luminal narrowing was not evident in most of these arteries.

Light microscopic examination of sections of plastic-embedded tissues revealed a number of features that were not detectable by study of ordinary histologic sections. These tissues, obtained at necropsy from three patients (Cases 1 to 3), were fixed with cold 3 percent glutaraldehyde in 0.1 molar phosphate buffer, postfixed with cold 1 percent osmium tetroxide in Millonig's phosphate buffer, and embedded in Maraglas®. Sections of these tissues, 1 μ thick, were stained with alkaline toluidine blue for light microscopic study. These preparations disclosed, in addition to clear cells, elongated or rounded cells that contained numerous dark cytoplasmic granules, referred to hereafter as *granular cells.* These cells were smaller and less frequent than clear cells and were most numerous in dense fibrous tissue in the A-V valves (Fig. 2d). They also were present in the myocardium (Fig. 6, a and b) and coronary arteries, but only in small numbers. They were not identifiable in sections stained with hematoxylin-eosin

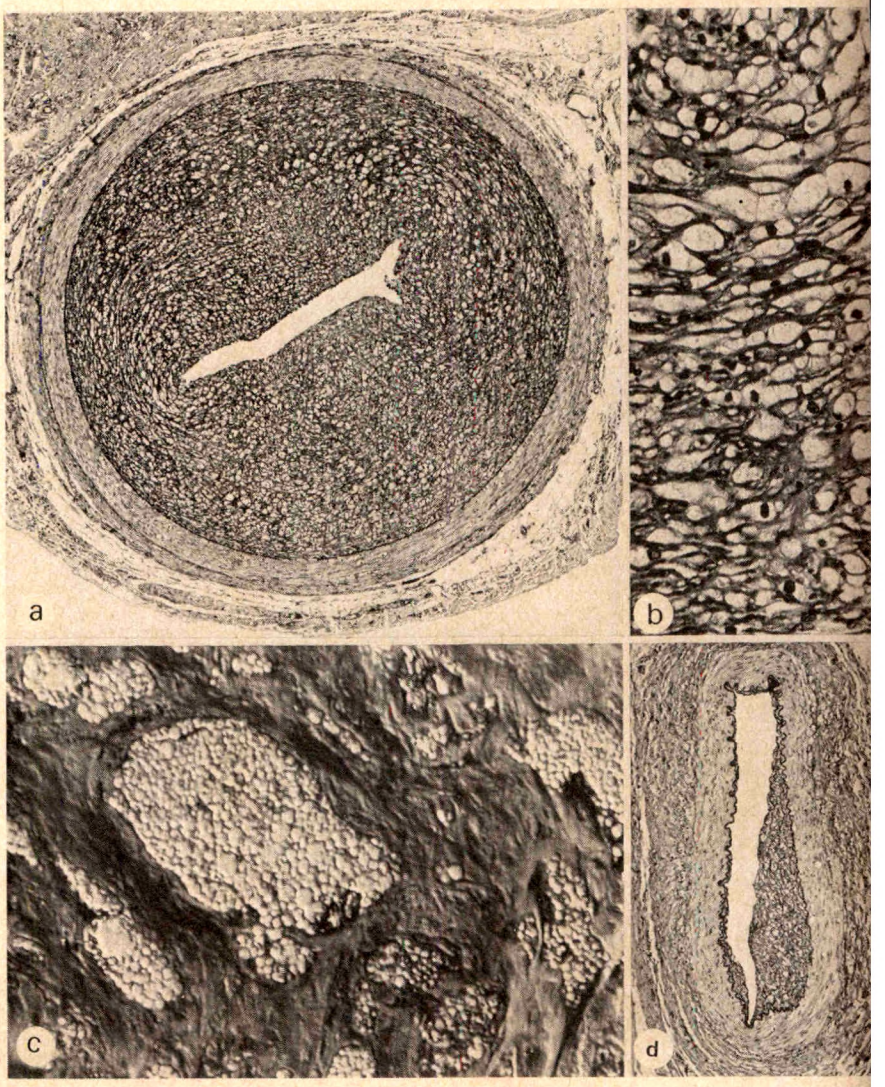


FIGURE 4. Histologic features of coronary arteries. **a,** Case 2. Cross section of greatly narrowed coronary artery. The intima is markedly thickened and contains many clear cells. The media is thin (Movat stain ×60). **b,** view of part of the intima of the same vessel at greater magnification. Note the increase in fibrous tissue and the vacuolization of the clear cells. **c,** Case 3. Clear cells in a semi-thin section of the coronary arterial intima, as seen with Nomarski interference contrast optics. The cytoplasm is occupied by fine vacuoles. Compare with the clear cells shown in the electron micrographs of Figures 7 and 10 (×1,600). **d,** Case 2. Small epicardial branch of coronary artery shows only focal intimal thickening. Compare with Figure 4a (Movat stain ×80). (Reduced by 35 percent.)

but were easily recognizable in sections stained with the periodic acid-Schiff (Fig. 3c) and Movat methods. Semi-thin sections of the coronary arteries revealed abundant intensely stained cytoplasmic inclusion bodies (up to 3 μ in diameter) in smooth muscle cells. Similar inclusion bodies were found in connective tissue cells of A-V valves and in cardiac muscle cells (Fig. 6, a to c). Although on light microscopic examination these inclusions resembled those in the granular cells, electron microscopic study showed (see later) that they had a completely different fine structure. Cardiac muscle cells in semithin sections also exhibited cytoplasmic clear vacuoles, which were difficult to observe in paraffin sections.

Ultrastructural Observations

The tissues of the three patients (Cases 1–3) studied by electron microscopy showed similar alterations. In agreement with the light microscopic observations, the most important changes in each patient were found in connective tissue cells, especially those in the intima of the coronary arteries and in the A-V valves. These connective tissue cells, including fibroblasts, smooth muscle cells, macrophages and cells whose type could not be identified, consistently contained cytoplasmic inclusions that varied in shape, size and internal structure but were limited by single, trilaminar membranes and resembled altered lysosomes. In some inclusions the

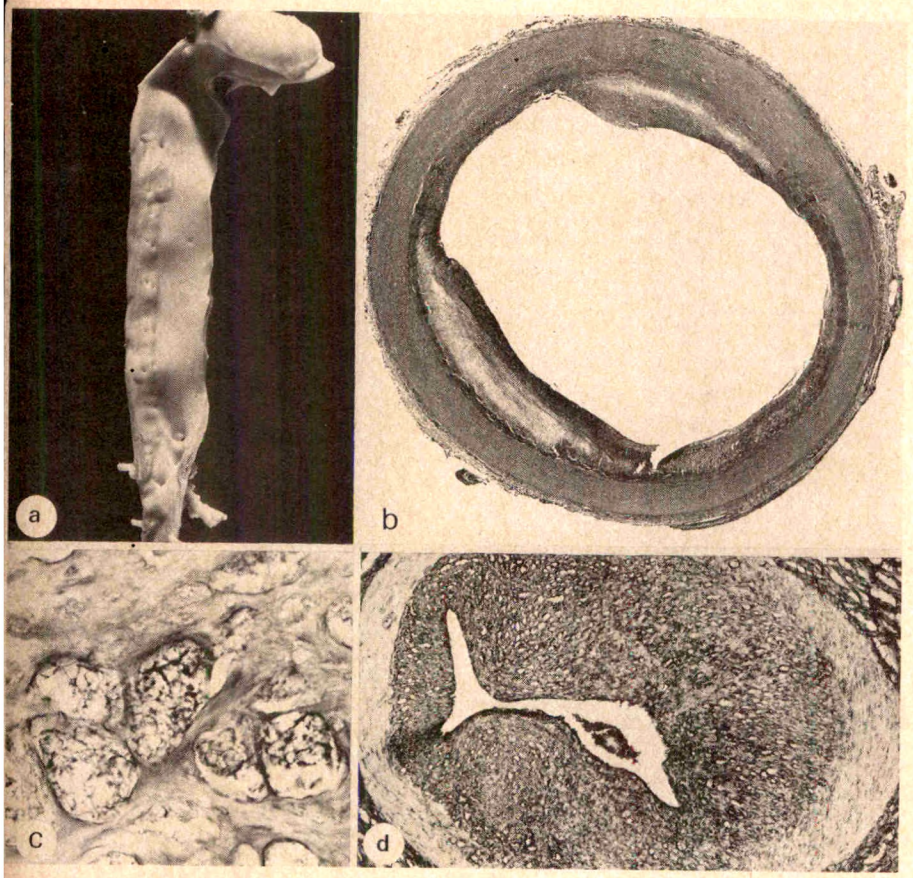


FIGURE 5. Views of aorta and small branch of hepatic artery. **a,** Case 1. Opened aorta showing raised plaques involving areas adjacent to orifices of intercostal arteries. **b,** Case 3. Low power view of cross section of aorta showing several large irregular fibrous plaques (hematoxylin-eosin stain × 9). **c,** Case 3. Clear cells are present in aortic intima (periodic-acid Schiff stain ×400). **d,** Case 2. Small branch of hepatic artery shows thickened intima and acid mucopolysaccharide deposits. The lumen is narrowed. (Colloidal iron stain ×100). (Reduced by 35 percent.)

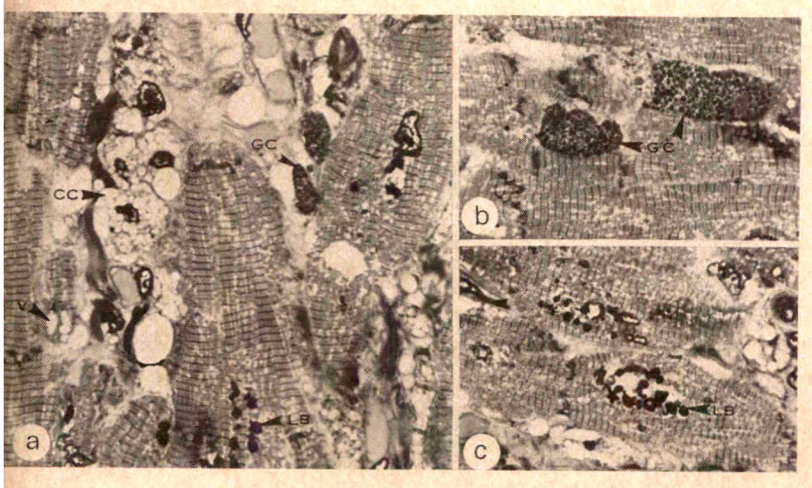


FIGURE 6. Case 3. **a to c,** semi-thin sections of plastic-embedded left ventricular muscle. Clear cells (CC) and granular cells (GC) are present in the myocardial interstitium. The cardiac muscle cells contain lamellar bodies (LB) and a few clear vacuoles (V) (toluidine blue stain ×800). (Reduced by 40 percent.)

limiting membranes were disrupted, and in others they were absent. The following four types of morphologically distinct membrane-limited inclusions were recognized: (1) clear, electron-lucent vacuoles; (2) lamellar bodies; (3) amorphous dense bodies; and (4) mixed bodies. Some cells contained almost exclusively one single type of inclusion, whereas others contained mixtures of different inclusions.

Clear vacuoles (Fig. 7): These occurred singly or in confluent masses, and measured from 0.1 to 3 μ in diameter. Most clear vacuoles either were completely empty or contained

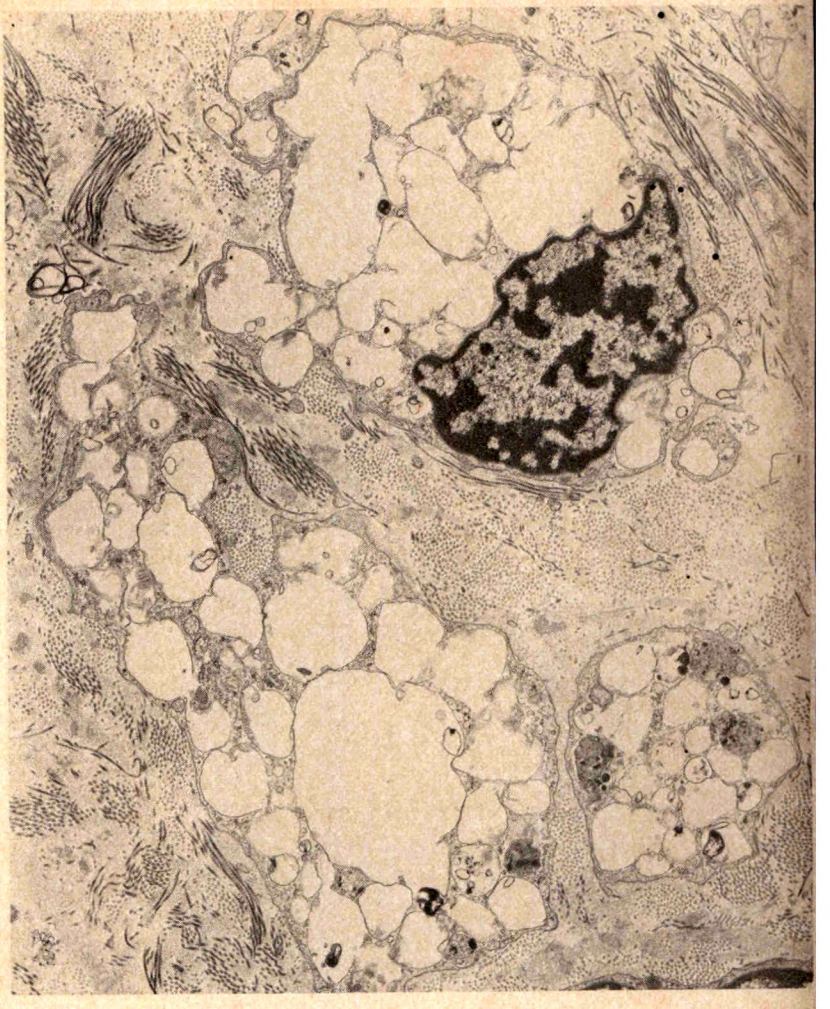


FIGURE 7. Case 3. Clear cells in the mitral valve are surrounded by collagenous and elastic fibrils. Note the indentations in the nucleus, the clear vacuoles limited by single membranes, and the occasional mixed inclusions (×10,450). (Reduced by 40 percent.)

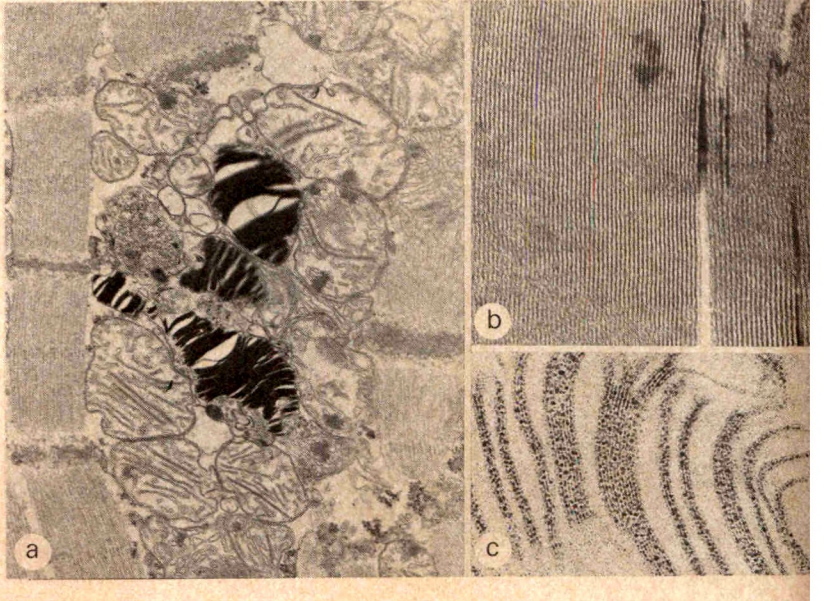


FIGURE 8. Case 3. Ultrastructure of lamellar bodies in myocardium (**a**) and coronary arteries (**b** and **c**). **a,** low magnification view showing several lamellar bodies surrounded by mitochondria and myofibrils (×24,000). **b,** high magnification view showing that the lamellar bodies are composed of alternating dark and light bands (×220,000). **c,** view as in **b,** but preparation stained by Thiéry method for demonstration of periodate-reactive carbohydrate materials. Each lamella appears as a row of minute electron-dense particles of silver (×170,000). (Reduced by 40 percent.)

scanty amounts of a finely granular or fibrillar, moderately electron-dense material. Cells in which the majority of these inclusions consisted of these vacuoles corresponded to the clear or gargoyle cells observed by light microscopy. These cells were rounded or elongated in shape and had eccentrically placed nuclei that were deeply indented by the cytoplasmic inclusions. Their plasma membranes were associated with a few pinocytotic vesicles. Basement membranes were absent. Ribosomes, cisterns of endoplasmic reticulum and 100 Å filaments also were present in these cells. Rarely, clear cells exhibited intercellular junctions of the zonula adherens type. Clear cells were most abundant in the intima of extramural coronary arteries and in valve subendocardium.

The lamellar bodies (Fig. 8, a to c): These were composed of electron-dense lamellae arranged concentrically or in parallel. The lamellae measured 35 Å in width and were separated from each other by lucent zones that measured 30 Å in width. When seen in transverse sections the lamellae showed faint serrations along their edges. Arrays of concentric lamellae were more frequent than those of parallel lamellae. Dense amorphous material also was observed in some lamellar bodies. Inclusions of this type were most abundant in medial smooth muscle cells of coronary arteries and in cardiac muscle cells. Ultrathin sections stained by the Thiéry method[44] for demonstration of periodate-reactive vicinal glycols (of the type present in carbohydrate materials) showed an intense reaction in the lamellar bodies (Fig. 8c). Clear vacuoles and amorphous dense bodies showed no reaction.

Amorphous dense bodies (Fig. 9, a and b): These were present in large numbers in the granular cells, but also were occasionally present in clear cells (Fig. 10) and in smooth muscle cells (Fig. 11c). These bodies were limited by single membranes and contained material that varied in density from one cell to another and even within a given inclusion. The most dense inclusions usually were either present in the center of the cell or composed of globular aggregates. Some inclusions also contained collagen fibrils with typical periodicity. Many of the collagen fibrils in these inclusions were more electron-dense than those in extracellular locations; a few, however, appeared more electron-lucent than normal but still retained their usual periodicity. Each inclusion usually contained a single fibril of collagen, but small aggregates of collagen fibrils were observed in some inclusions. The plasma membranes of the granular cells often exhibited irregular outlines and broad invaginations that contained electron-dense material similar to that present in the membrane-bound structures within the cells. A few pinocytotic vesicles were also observed. The cytoplasm of the granular cells contained small numbers of free ribosomes, elements of smooth and rough endoplasmic reticulum, mitochondria, microtubules (200 Å in diameter) and

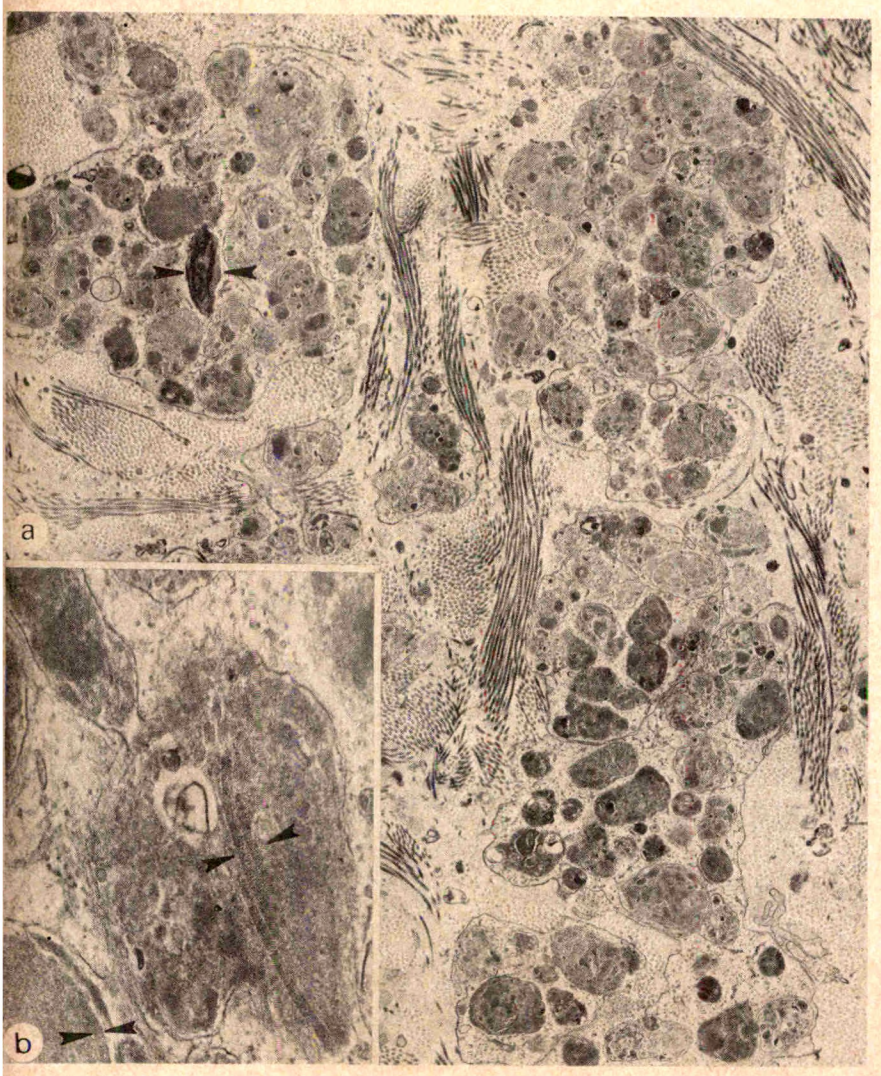


FIGURE 9. Case 3. Granular cells in tricuspid valve. **a,** low power view of cluster of granular cells surrounded by dense collagenous tissue. These cells contain numerous dense bodies composed of amorphous to globular material. Similar dense bodies are free in the extracellular space. Note the collagen fibrils **(arrowheads)** in one of the intracellular dense bodies. **b,** several collagen fibrils **(arrowheads)** with typical periodicity are present in the dense bodies of the granular cells (×66,500). (Reduced by 35 percent.)

peripherally located filaments (50 Å in diameter). In some cells the filaments were closely applied to the inner aspect of the plasma membranes. Golgi zones were not evident and nuclei were encountered only rarely. Intercellular junctions that consisted of small zonulae adherentes were evident between cytoplasmic processes of adjacent granular cells. Ultrastructural study confirmed the presence of small numbers of granular cells in myocardium and coronary arteries, but failed to disclose collagen fibrils within inclusions of the granular cells in these sites.

Mixed bodies (Fig. 7 and 10): These consisted of membrane-bound inclusions that contained different kinds of material and were present in all tissues examined. These bodies contained round or irregularly shaped groups of lamellae and globular, amorphous, finely granular or fibrillar material of moderate density.

Myocardial alterations: Cardiac muscle cells were mildly hypertrophied in all three patients. The nuclei were irregular in shape and appeared vacuolated because of peripheral clumping of chromatin. Mitochondria of cardiac muscle cells in all three patients showed clear matrixes, disruption of the cristae and loss of intramitochondrial granules; in Case 3 some muscle cells exhibited increased density of mitochondrial cristae and flocculent material in the mitochondrial matrixes. All of these changes were considered to result from postmortem autolysis.

The most distinctive alteration in cardiac muscle cells consisted of the presence of lamellar bodies that measured from 1 to 3 μ in size and occupied less than 5 percent of the cell volume (Fig. 6, a and c, and 8, a to c). Clear vacuoles, however, also were present in cardiac muscle cells. They did not have a characteristic localization and they did not appear to be related to the sarcoplasmic reticulum or Golgi complexes, which were normal. Fibroblasts and macrophages in myocardial interstitium contained large numbers of clear vacuoles in their cytoplasm (Fig. 6, a to c). These inclusions were closely packed and it was often impossible to distinguish the fine structure of other cellular organelles. The organization of the collagen fascicles was generally preserved; however, irregularly arranged bundles of collagen, with occasional loss of periodicity, were identified in myocardial interstitium. Destruction of collagen fibrils was not observed. Spiney collagen (Fig. 12a) with features similar to those described by Banfield et al.[45] was present in the myocardial interstitium of Patients 1 and 2 and in the coronary arterial intima of Patients 2 and 3. Cross-striated banded structures of the type described by Sun and White[46] were present in myocardial interstitium in Patient 1. These structures (Fig. 12b) had a periodicity of 1,000 Å, and had parallel fine fibrils between the dark bands. Both the spiney collagen fibrils and the cross-striated banded structures were seen mainly in perivascular areas, where they formed small bundles.

Valve alterations: The changes observed were more severe in the mitral than in the tricuspid valve but were morphologically similar. Large cells containing numerous clear vacuoles (Fig. 7) were observed throughout the whole thickness



FIGURE 10. Case 3. Ultrastructure of mixed inclusions. Cell with small eccentrically located nucleus, numerous clear vacuoles, moderate numbers of mixed inclusions and a few lamellae is present in tricuspid valve. Compare with Fig. 7 (×11,600). (Reduced by 40 percent.)

of the leaflets, although they were most abundant in the proximal two thirds of the valves and in the fibrous anuli. Many cells also contained lamellar and mixed bodies (Fig. 10). Granular cells were observed in areas in which the connective tissue stroma was densest and richest in collagen fibrils. The stroma of the A-V valves was composed of closely packed collagen fibrils embedded in a ground substance that contained fine fibrils and small electron-dense spicules considered to be composed of precipitated acid mucopolysaccharides. Microfibrils and small elastic fibers were observed between the collagen bundles; these elements were surrounded by ground substance that showed greater than normal electron density. It was not uncommon to observe unorganized bundles of collagen coursing in various directions. This increase in fibrous tissue was generalized, although it was most prominent in the basal and middle thirds of the valves. Spiney collagen or cross-striated banded structures of the type present in myocardial interstitium were not found in the A-V valves of any of the three patients.

The calcified basal portion of the mitral valve of Patient 3 showed large aggregates (up to 4,000 Å in diameter) of highly electron-dense precipitates of granular or finely fibrillar material (Fig. 12c). Needle-shaped structures resembling crystals often were observed in the periphery of these aggregates. Cells in these areas showed disruption and fragmentation. The interstitial space in calcified areas (Fig. 12d) had a striking vacuolar appearance and contained deposits of lipid-like material and myelin figures (concentric lamellae of irregular arrangement and periodicity). Collagen fibrils in these sites showed degenerative changes consisting of fragmentation and loss of their periodic cross-banding. Nevertheless, the process of calcification did not involve the collagen fibrils themselves. Elastic fibers also showed fragmentation, and in some areas were associated with crystalline or needle-shaped deposits of calcium (Fig. 12d).

Coronary arterial changes: The thickening of the coronary arterial intima was attributable both to the presence of large numbers of clear cells and to a substantial increase in collagen fibrils. Also present in the coronary intima were many smooth muscle cells that contained numerous clear vacuoles, a few lamellar bodies and only scanty peripherally located contractile elements (Fig. 11a). These cells also had considerably thickened basement membranes. Dense collagen bundles of normal size and periodicity surrounded the clear cells and the smooth muscle cells. The interstitial space also contained spiney collagen and large deposits of moderately electron-dense material resembling that found in basement membranes (Fig. 12a). These deposits were associated with numerous microfibrils and with collagen or elastic fibers. Accumulations of electron-dense granules and fine spicules of acid mucopolysaccharides also were present in these areas.

The smooth muscle cells in the medial layers of the coronary arteries had thickened basement membranes and contained many pinocytotic vesicles associated with their plasma membranes. Most of these smooth muscle cells contained large

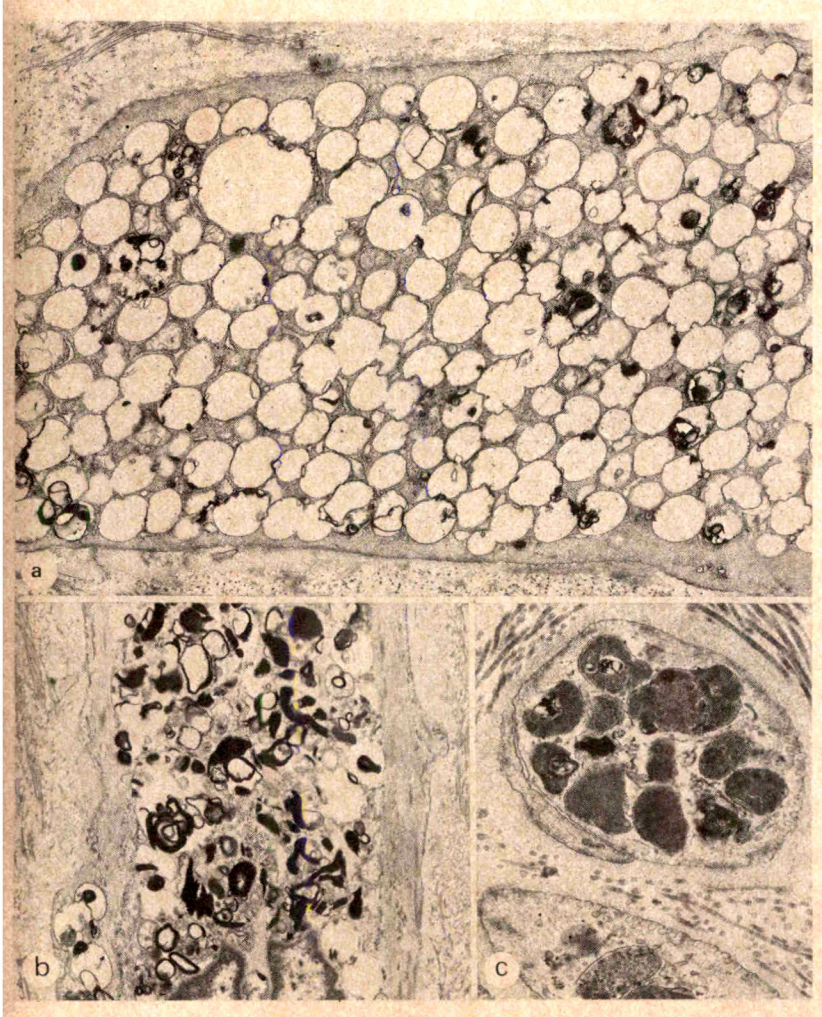


FIGURE 11. Case 3. Smooth muscle cells in intima (**a**) and media (**b** and **c**) of coronary arteries. **a,** most of the cytoplasm of this cell is occupied by clear vacuoles; a few lamellae are present also. The few contractile elements that remain are displaced to the periphery. Small spicules of material considered to be acid mucopolysaccharides are present in the interstitium(×15,850). **b,** this medial cell contains mostly lamellar bodies of the type shown in Fig. 8 (×10,450). **c,** amorphous dense bodies, similar to those in granular cells, are present in these medial smooth muscle cells (×28,000). (Reduced by 40 percent.)

amounts of lamellar bodies (Fig. 11b) that corresponded to the dark inclusions observed in semi-thin sections stained with toluidine blue. Clear vacuoles and amorphous dense bodies (Fig. 11c) also were present in medial smooth muscle cells, but were less numerous than the lamellar bodies.

Discussion

Valve Disease

Valve involvement in the Hurler syndrome consists of proliferation of fibrous tissue that contains diverse types of abnormal cells, mainly clear cells and granular cells, and ground substance with increased amounts of acid mucopolysaccharides. Although involvement of all four valves has been described in a few patients with the Hurler syndrome,[43] all four were involved in each of our five patients. The valve lesions consist of generalized thickening that is most marked, at least in the A-V valves, at the margins, which may be nodular and irregular. The thickening of the leaflets usually is accompanied by thickening and shortening of the chordae tendineae. Although the valve involvement in these patients may have no functional consequences, some degree of valve regurgitation may occur. When present, this alteration usually is limited to the mitral or aortic valve, or both.[42,43,47] Although regurgitation is the predominant mitral valve lesion at necropsy,[42,47] mitral stenosis has also been reported.[48,49] Systolic murmurs have been described in many patients with the Hurler syndrome.[47] Hemodynamic observations, however, have been reported rarely. Krovetz et al.[47] demonstrated with angiography valve (mitral, aortic or pulmonary) regurgitation in 3 of 11 children with the Hurler syndrome.

The results of our ultrastructural studies of mitral and tricuspid valves confirm and extend the observations of Lagunoff et al.,[10,30] who observed clear and granular cells in the mitral valve. The clear cells in the valves appear similar to those in other tissues of patients with the Hurler syndrome. We consider these cells to be histiocytes or fibroblasts, or both, distended by intralysosomal deposits of acid mucopolysaccharides that are highly soluble and are lost from tissues during dehydration and embedding. The origin of the granular cells is unclear. We found intracellular deposits of collagen in granular cells in cardiac valves, but not in granular cells in myocardial interstitium or coronary arteries. It is likely that these cells are fibroblasts that contain intracellular deposits of collagen that has undergone either autophagy or heterophagy.[50] It is unclear whether all of the granules of these cells contain partially altered or amorphous deposits of collagen or collagen-acid-mucopolysaccharide complexes. From our

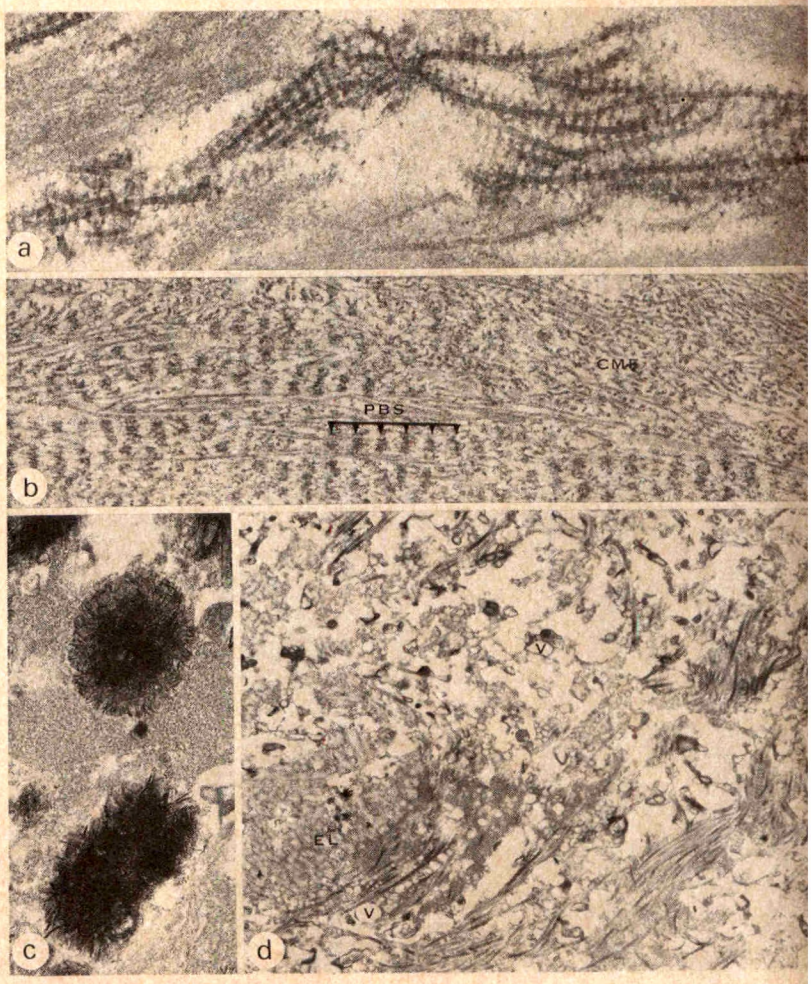


FIGURE 12. Connective tissue changes. **a,** Case 3. Bundles of fibrils of spiney collagen are associated with basement membrane-like material in coronary intima (×53,000). **b,** Case 1. Connective tissue microfibrils (CMF) in myocardial interstitium are adjacent to periodic banded structures (PBS) composed of dark bands connected by fine filaments (×56,750). **c,** Case 3. Aggregates of electron-dense needle-like deposits of calcium are present in the calcified area of the mitral valve ring (×65,000). **d,** same area of valve ring showing spicules of calcium associated with disrupted elastic fibers (EL); small electron-dense lamellae, and clear spaces considered to be lipid vacuoles (V) (×17,000). (Reduced by 40 percent.)

studies we conclude that the valve deformities result not only from infiltration with clear and granular cells but also from excessive deposition and abnormal molding of collagen. In this respect we regard the abnormalities of the valves as similar to those in the cornea, skin and skeletal system, in which abnormal organization of fibrous tissue may also play a major pathogenetic role.

Anular and valve calcification: Calcification of the valves has been described in at least seven necropsy cases of the Hurler syndrome,[26,27,43,51] but information concerning the fibrous valve anulus was not given in these reports. Mitral anular calcific deposits were observed in three of our five patients. Small calcific deposits also were present on the ventricular aspect of the anterior mitral leaflet and on the aortic aspect of the aortic valve cusps in each of these three patients. Nonnflammatory calcification of the mitral anulus in children is rare and usually occurs only in the Hurler and Marfan syndromes.[52] Disturbances in metabolism of acid mucopolysaccharides occur in both syndromes. Some aspects of the mechanisms of calcification of biologic tissues are unclear. Different studies[53–58] suggest that mitochondrial and lysosomal factors, lipids, chondroitin sulfate, collagen and elastic fibers are involved in forming of loci of calcification. Unfortunately, most of these studies have been made in skeletal tissue, and studies concerning calcification of the human mitral anulus are based only on histologic and histochemical observations.[59–61] Many etiologic factors have been postulated. It appears that the first metabolic step in the process of sclerosis and calcification in mitral anulus is a mesenchymal reaction in which the cells synthesize acid mucopolysaccharides, collagen and elastic fibers.[59–61] Calcification of the valves is associated with sclerotic changes.[61,62] The state and importance of acid mucopolysaccharides in degenerative processes is controversial. During the aging process the ratio of the content of dermatan sulfate to that of hyaluronic acid increases in cardiac valves,[63,64] aorta[65,66] and skin.[67,68] These biochemical alterations resemble those occurring in patients with the Hurler syndrome because of their tissue deposits of dermatan and heparan sulfate. It appears that acid mucopolysaccharides play an important role in the production of sclerosis and calcification of the cardiac valves. As discussed elsewhere,[50] increased amounts and altered proportions of these compounds may alter the synthesis of collagen.

We observed large deposits of acid mucopolysaccharides, lipid-like material, myelin figures and degenerated cells in the calcified mitral anulus of Patient 3. Degenerative changes in collagen and elastic fibers were also present in this area. Elastic fibers were closely associated with needle-shaped precipitates, as observed in other diseases in which pathologic calcification occurs.[69] Our observations, which constitute the first ultrastructural study of mitral anular calcification, are in agreement with the ultrastructural findings of Kim and Huang[70] on calcified human aortic valves. It would appear, therefore, that the processes of calcification of the aortic valve and mitral anulus are associated with similar morphologic changes in connective tissue components.

Coronary Arteries

A remarkable alteration of the cardiovascular system in the Hurler syndrome is the severe involvement of the coronary arteries. All five of our patients had luminal narrowing greater than 75 percent in one or more of the three major arteries. This narrowing was mainly due to thickening of the intima. The intramural coronary arteries also were involved, but to a lesser degree.

Acid mucopolysaccharides and atherosclerosis: The presence of acid mucopolysaccharides in the normal arterial wall, mainly in the intima, has been documented by Berenson et al.[71,72] Interest in the role of these compounds as possible pathogenetic factors in human atherosclerosis is supported by several observations. As mentioned, significant changes occur in the ratios of different acid mucopolysaccharides in aging blood vessels. These changes may account partially for the concomitant increase in the calcium content of the aorta[65] and may be responsible for the intimal thickening.[73] The atherogenic role of acid mucopolysaccharides is also supported by the storage of these substances in atheromatous lesions and by the known affinity of low density and very low density lipoproteins for acid mucopolysaccharides, with which they form insoluble complexes (see[74,75] for review). The stability or reversibility of these complexes may be related to calcium binding.[74,75] Furthermore, electrophoretic studies[76] have suggested that alterations in the relative proportions of different acid mucopolysaccharides are more important in atherogenesis than are changes in total quantity. The preceding observations suggest that acid mucopolysaccharides play an important role in the production of atherosclerosis in children with the Hurler syndrome. Similar considerations may apply to the atherosclerotic lesions that develop in patients with other mucopolysaccharidoses.

Preferential coronary involvement in Hurler's syndrome: The reason for the preferential involvement of the coronary arteries, as compared with other arteries, in the Hurler syndrome is unclear. We consider it likely that the metabolic alterations cited lead to an exaggeration of the proliferative process that normally occurs in the coronary arterial intima in children. Despite the severe narrowing of the coronary arteries, thrombi were not observed. Likewise, cardiac mural thrombi were not observed in any of our five patients, even though the mural endocardium was thickened in all four chambers in each patient. It is possible that the deposits of dermatan and heparan sulfate compounds, which have anticoagulant activity resembling that of heparin,[77,78] play a role in preventing thrombus formation.

Important structural differences exist between the atherosclerotic plaques in coronary arteries in adults and the intimal fibrosis and deposition of acid mucopolysaccharides in clear cells and smooth muscle cells of coronary arteries of children with the Hurler syndrome. In the latter, deposits of cholesterol and other lipids are practically absent. Conversely, the thickening of the intima is more focal in adults with atherosclerosis. For reasons that remain unclear, in our patients with the Hurler syndrome the aortic intimal plaques were much

less cellular and more fibrotic than the lesions in the coronary intima. These aortic plaques contained some calcific deposits and cholesterol and resembled those in adults with atherosclerosis, even though they also contained small numbers of the clear cells typically found in the Hurler syndrome.

The number of cytoplasmic inclusions is much larger in intimal than in medial smooth muscle cells, and the latter cells have primarily lamellar bodies, whereas the intimal cells accumulate mainly clear vacuoles. The reasons for this discrepancy and for the relative sparing of intramural coronary arteries are not known.

Lamellar inclusion bodies: The lamellar bodies observed in smooth muscle cells in the coronary arteries and in cardiac muscle cells are similar to those described in other tissues, including the liver, brain, cornea and skin of patients with the Hurler syndrome.[11,30–35] In our study, the lamellar bodies gave a positive Thiéry reaction, in which each lamella appeared as a row of closely spaced silver granules. Like a positive periodic acid-Schiff reaction, a positive Thiéry reaction is indicative of the presence of periodate-reactive vicinal glycol groups.[44] This suggests the presence of carbohydrate materials. The lamellar bodies in the Hurler syndrome have been considered to represent deposits of glycolipids, possibly gangliosides.[11] Biochemical studies[6–8] have shown increased content of gangliosides in the brain, liver and spleen of patients with the Hurler syndrome. It is possible that these gangliosides accumulate as a result of deficiency of beta-galactosidase.[14,21] Lamellar bodies resembling those in the Hurler syndrome also occur in a variety of tissues in other pathological conditions, including Tay-Sachs disease, Sandhoff's disease, Sanfilippo's disease, GM_1 gangliosidosis and Fabry's disease.[79,80] The differences between the types of gangliosides or ceramide hexosides that are stored in these diseases are not sufficient to produce structures that are morphologically distinctive for each of these disorders.[81] In cardiac muscle cells, lamellar bodies similar to those described in this study have been reported only in Fabry's disease.[82]

Myocardium

Causes of myocardial failure: An adequate explanation has not been given for the sudden cardiovascular collapse or progressive congestive cardiac failure that may occur. Together they account for about 50 percent of the deaths of patients with the Hurler syndrome.[40,47] The sudden cardiovascular collapse is probably a manifestation of ischemic heart disease. The congestive heart failure is probably the result of a combination of factors, including coronary insufficiency, deposition of acid mucopolysaccharides and glycolipids in myocardium, respiratory dysfunction, systemic hypertension, cardiac valve disease, and anemia and hypoproteinemia related to malnutrition and hepatic disease. We observed clear cells and granular cells in the myocardial interstitium and accumulation of clear vacuoles and lamellar bodies in cardiac muscle cells. The clear cells were numerous, but difficult to detect by light microscopy. It seems likely that these cells and the increased amounts of interstitial fibrous tissue impart to the myocardium its characteristic firm consistency. Such a consistency probably results in reduced compliance. The abnormal interstitial cells and the deposits within cardiac muscle cells do not appear to be sufficiently numerous to account for the cardiac dysfunction. Similarly, the valve involvement, although it appears to be a striking anatomic finding, is in itself an inadequate explanation for the congestive heart failure in these patients.

Myocardial hypoxia is the most likely principal factor causing the myocardial failure. Previous histologic studies of the heart have disclosed evidence of myocardial necrosis in only one patient with the Hurler syndrome,[28] even though clinical and pathologic studies suggest that ischemic heart disease does occur in this syndrome. It seems reasonable to believe that some patients with the Hurler syndrome have had a myocardial infarction but have died too soon for recognizable changes to have been evident on histologic study. Consideration also must be given to the possibility that the gradual progression of the coronary arterial narrowing may have served as stimulus for the development of collateral vessels. Since the latter vessels are smaller than the extramural coronary arteries they would be less likely to be involved by the glycolipid and acid mucopolysaccharide deposits and would have provided a certain degree of protection against ischemia. Systemic hypertension (blood pressure greater than 140/90 mm Hg) is frequently found in patients with the Hurler syndrome (present in 9 of the 15 patients studied by Krovetz et al.[47]) and was definitely present in two of our five patients. Its cause is unknown.

Conclusions

We conclude:

1. All four cardiac valves and the mural endocardium of all four cardiac chambers are thickened in patients with the Hurler syndrome.
2. Involvement of the valve leaflets, anuli and chordae tendineae is characterized by increased amounts of collagen and by infiltration with clear cells and granular cells.
3. Involvement of the myocardium is manifested by the presence of clear and granular cells in myocardial interstitium and of lamellar bodies and occasional clear vacuoles within cardiac muscle cells. The cardiac failure that occurs in patients with the Hurler syndrome is considered to result from a combination of factors including reduced myocardial compliance due to infiltration with clear and granular cells, interstitial fibrosis and deposition of storage materials in cardiac muscle cells; valve deformities; coronary arterial narrowing; systemic hypertension; anemia; hypoproteinemia; and respiratory dysfunction.
4. Disease of the extramural coronary arteries is severe and due to marked intimal thickening. This thickening results from increased amounts of collagen and from the presence of large numbers of clear cells and smooth muscle cells, both of which are distended by acid mucopolysaccharide deposits. Medial smooth muscle cells are less involved and contain mostly lamellar bodies.

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Echocardiographic Evaluation of Tricuspid Valve Endocarditis

An M Mode and Two Dimensional Study

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Standard M mode echocardiography and a new real time two dimensional echocardiographic imaging system were utilized to follow the progressive anatomic destruction of the tricuspid valve in a patient with bacterial endocarditis. The initial two dimensional echocardiographic study revealed large vegetative masses attached to severely prolapsing tricuspid leaflets. Serial studies demonstrated eventual disruption of the chordal attachments of the anterior tricuspid leaflet resulting in frank leaflet flail. This technique was seen to complement both M mode echocardiography and cardiac angiography by providing spatial information concerning serial changes in the disordered tricuspid valve. Such findings call attention to the relative roles of various diagnostic measures, including M mode and two dimensional echocardiography, in assessing the specific anatomic and functional performance of a diseased tricuspid valve.

Destruction of the tricuspid valve as a result of infective endocarditis may lead to severe tricuspid insufficiency and right heart failure. Although right ventricular angiography may provide important information about the right ventricle and pulmonary valve, in the presence of massive tricuspid insufficiency anatomic details of the tricuspid valve may be obscured by the rapid, dense and simultaneous opacification of the right atrium and right ventricle. This report describes the relative clinical value of M mode and two dimensional echocardiography in delineating serial changes in the anatomic configuration of the tricuspid valve in a patient with bacterial endocarditis.

Methods

M mode echocardiograms were performed with the patient in the slight left lateral position using previously described techniques.[1] A commercially available ultrasonoscope, equipped with a continuous recorder and a 2.25 megahertz, 7.5 cm focused transducer, was utilized. M mode studies were performed within 1 hour of the two dimensional echocardiographic studies.

Two dimensional (cross-sectional) echocardiograms were obtained using a previously described[2,3] real time imaging device developed in the Duke University Biomedical Engineering Department and currently undergoing clinical evaluation in the Duke University Department of Medicine. This imaging system uses a contact, hand-held 16 element transducer array that measures 14 by 24 mm at the site of skin contact. The system relies upon phased array principles to steer the sound beam electronically through the structures being studied. High resolution, real time tomographic images of cardiac structures are presented in a circular sector format, 60° or 90° in azimuth. This prototype imaging system is undergoing continual changes to improve image quality. At present, the quality of images in the 90° sector format (see Fig. 2) appears to be superior to that of images previously obtained in the 60° format (see Fig. 4 and 6).

Images are permanently recorded on video tape for later playback and analysis. The images presented in this report are 35 mm still photographic recordings of single frame images from video tape. There is thus a loss of the visual integration of motion normally seen with the real time recording as well as a severe degradation in image quality caused by the video tape recording process. An individual field from the tape recording represents only 1/60th of a second. When operating

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in the 128 line format, therefore, each single frame visual field represents only half (or 64 lines) the information provided in the actual scan or in real time playback. The primary purpose of the schematic diagrams used herein (see Fig. 2, 4 and 7) is to enhance understanding of the stop frame, two dimensional echo images presented.

Normal tricuspid valve: Figure 1 schematically shows the planes of view for examination of the long axis of the left ventricle (position I) and the tricuspid valve (position II). The plane of the sector arc in position II intercepts the right atrium, the long axis of the tricuspid valve and the inflow portion of the right ventricle. This plane is usually obtained by rotating the transducer in a counterclockwise direction from the plane suitable for examination of the long axis of the left ventricle. Systolic and diastolic single frame photos of a normal tricuspid valve are shown in Figure 2. Simultaneous visualization of tricuspid and mitral structures is not always possible.

Case History

A 17 year old black youth had had a heart murmur since birth. Cardiac catheterization at age 7 years revealed a ventricular septal defect with a pulmonary to systemic blood flow ratio of 2.6:1. Corrective surgery was refused at that time, and the patient remained completely free of cardiovascular symptoms in the intervening period. In the 2 months before his present admission, he noticed intermittent fever associated with progressive weakness, shortness of breath and swelling of the legs.

Significant physical findings on admission included an ill-appearing young man in acute respiratory distress with a respiratory rate of 35/min. There was marked neck vein and liver distension with massive pitting edema over both the presacral area and legs. The blood pressure was 160/100 mm Hg and the heart rate was 110 beats/min and regular. The point of maximal impulse was felt in the sixth left intercostal space at the level of the anterior axillary line. The first heart sound was accentuated and the second sound was normally split. There were easily audible presystolic and protodiastolic gallops. A grade 3/6 rough pansystolic murmur heard alon the left sternal border radiated to the ventricular apex. grade 4/6 holosystolic blowing murmur (accentuated on in spiration) was heard maximally over the lower right sterna border.

Pertinent laboratory data on admission included an elec trocardiogram revealing normal sinus rhythm, left axis de viation and incomplete right bundle branch block. Ches X-ray films showed generalized cardiomegaly, pulmonar edema and nodular infiltrates in the right upper pulmonar lobe. The white blood count was 39,500/cm^3 with a marke shift to the left.

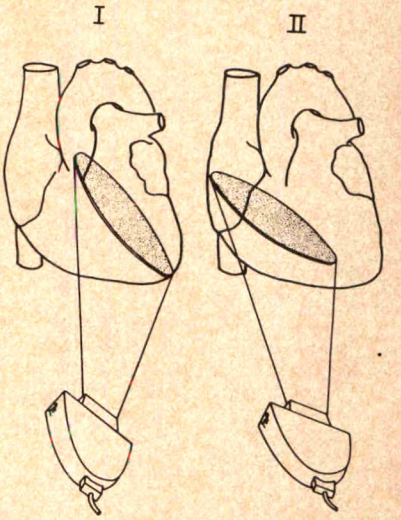


FIGURE 1. Schematic representation of the planes of the two-dime sional scans used to examine the long axis of the left and right vent cles. **I,** plane through the long axis of the left ventricle. The aortic ro is at the top and the ventricular apex is near the bottom. **II,** plane throug the right atrium, tricuspid valve and inflow portions of the right vent cle.

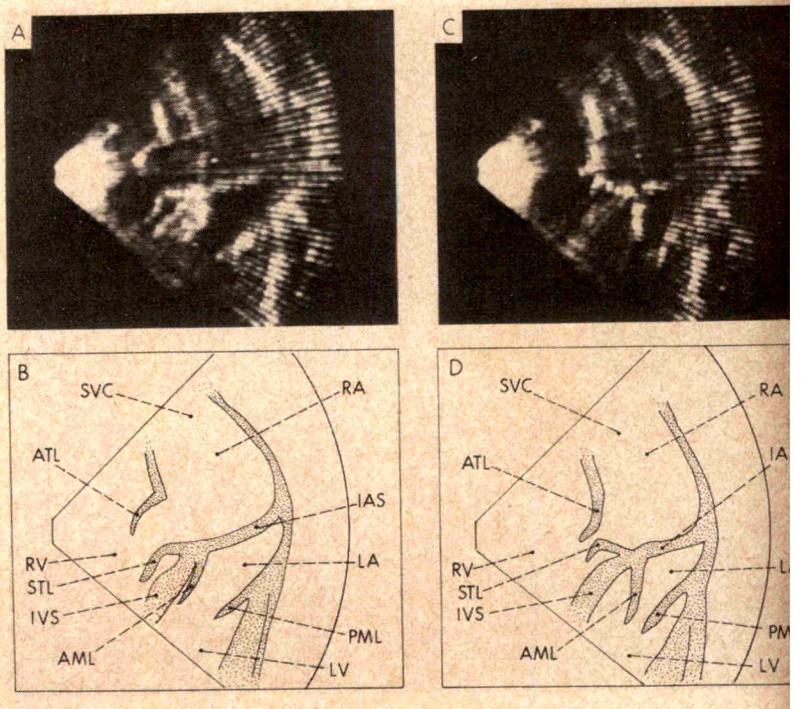


FIGURE 2. Single frame photographs and matched schematic diagrams of a two dimensional scan indicating the structures seen in a normal patient through position II. **A** and **B,** open tricuspid valve in diastole. The right atrium is seen in the upper portion of the scan; the inflow portions of the right ventricle are seen to the lower left. Anterior is to the left of the photograph. The atrial septum may occasionally be visualized in this view. **C** and **D,** systolic frame from the same patient showing the closed tricuspid leaflets. AML = anterior mitral leaflet; ATL = anterior tricuspid leaflet; IAS = interatrial septum; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PML = posterior mitral leaflet; RA = right atrium; RV = right ventricle; STL = septal tricuspid leaflet; SVC = superior vena cava.

A standard M mode echocardiogram showed mild left ntricular dilatation, paradoxical septal wall motion, peri-rdial effusion and marked thickening of the visualized rtions of the tricuspid leaflet (Fig. 3). Because tricuspid lve disease was documented with M mode echocardiography ortly after admission preparations for placing a pressure onitoring catheter into the pulmonary artery were not ntinued.

A two dimensional echocardiogram revealed similar find-gs and, in addition, demonstrated marked prolapse of the terior tricuspid leaflet in systole (Fig. 4). The mass of echoes n on the anterior tricuspid leaflet was believed to represent arge vegetative mass. A two dimensional sonographic ex-mination of the inferior vena cava revealed this structure to be markedly dilated and hyperpulsatile. Blood cultures obtained on admission later demonstrated alpha hemolytic streptococci (Group H antigen, Streptococcus sanguis) sensitive to penicillin G.

Therapy was initiated with digoxin, 0.25 mg daily and furosemide, 80 mg daily; penicillin G, 3 million units intravenously every 6 hours; and streptomycin, 0.5 intramuscularly daily. After a several week period of clinical instability due to the complications of acute glomerulonephritis and transient renal failure, septic pulmonary emboli, thrombocytopenic hemolytic anemia and major motor seizures, the patient's condition began to improve satisfactorily. Right ventricular failure was brought under control leaving the patient mildly short of breath but with residual clinical evidence of massive

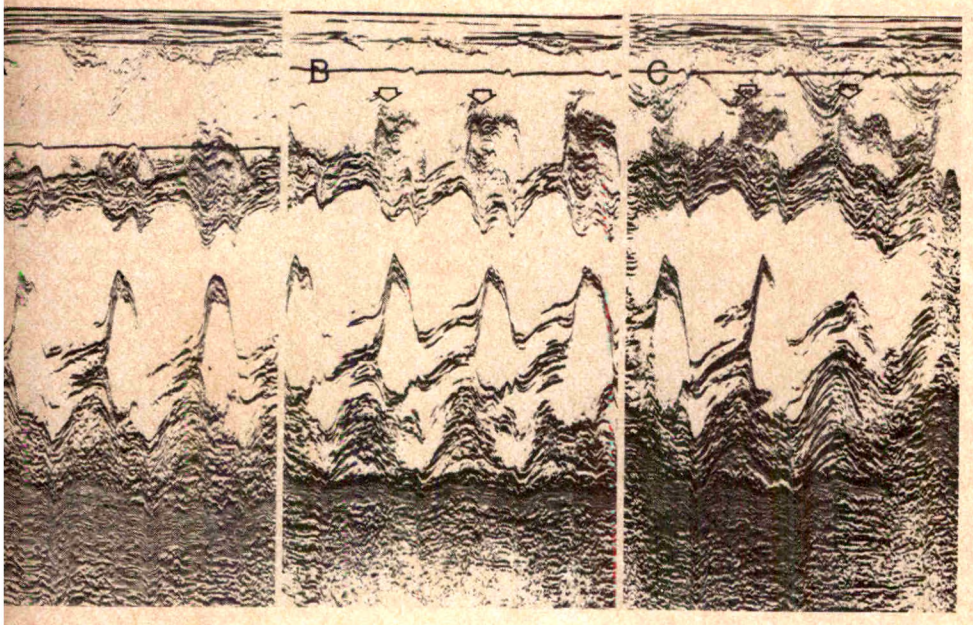


FIGURE 3. Time-motion (M mode) echocardiograms through the left ventricle taken on admission. Echoes in **A, B** and **C** were taken with progressive slight medial angulation of the transducer in order to visualize more adequately the tricuspid valve. **Arrows** in **B** and **C** indicate the abnormal tricuspid valve echoes. Septal wall motion is abnormal, and a small pericardial effusion is seen.

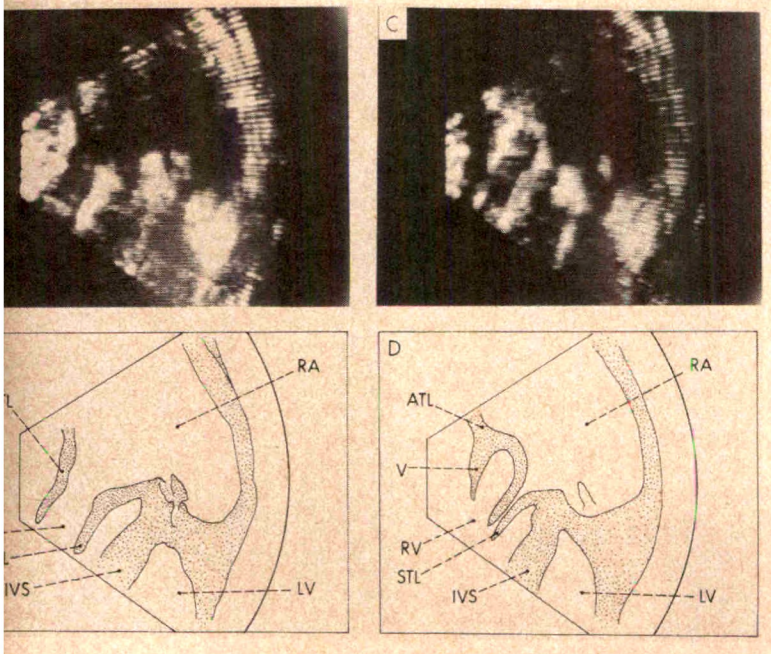


FIGURE 4. Single frame photos and matched schematic diagrams from the two dimensional scan through position II taken on admission. **A** and **B,** open tricuspid leaflets in diastole. **C** and **D,** severe prolapse of the anterior tricuspid leaflet (ATL) in systole. A vegetative mass (V) is attached to the anterior tricuspid leaflet. Abbreviations as in Figure 2.

tricuspid insufficiency characterized by a dilated hyperpulsatile liver, 2+ pitting edema of the legs and a grade 4/6 holosystolic murmur that increased on inspiration.

An M mode echocardiogram 8 weeks after admission (*Fig. 5*) showed resolution of the pericardial effusion. Paradoxical septal wall motion compatible with right ventricular volume overload was again noted. The anterior leaflet of the tricuspid valve was easily visualized and demonstrated a marked increase in amplitude that was accompanied by high frequency vibrations in diastole and coarse movements in systole. The two dimensional echocardiogram of the tricuspid valve (Fig. 6) showed frank systolic flail of the anteriorly positioned tricuspid leaflet. During examination of the heart in the long axis of the left ventricle, this leaflet was seen to move high into the pulmonary outflow tract in diastole. The mass previously attached to this leaflet (Fig. 4) was now absent. Examination of the abdomen showed the inferior vena cava to be more dilated and pulsatile than before.

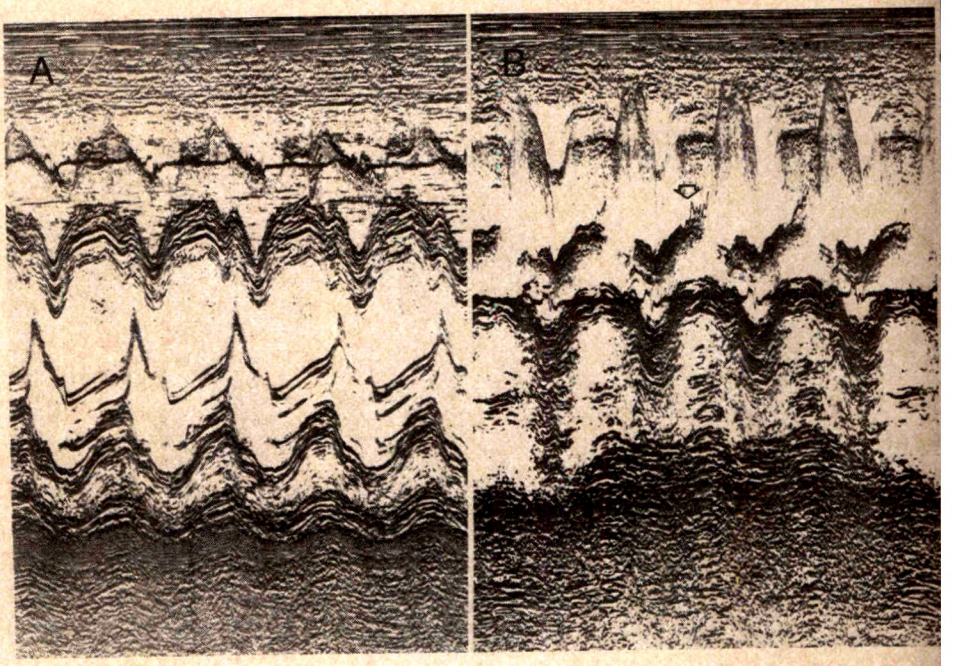


FIGURE 5. Time-motion (M mode) echocardiograms taken 8 weeks after admission. **A,** abnormal septal wall motion from the scan through the left ventricle. Abnormal echoes from the tricuspid valve can be seen within the right ventricle. **B,** medial angulation of the transducer showing the marked amplitude of excursion and coarse systolic vibrations of the anterior tricuspid leaflet **(arrow).**

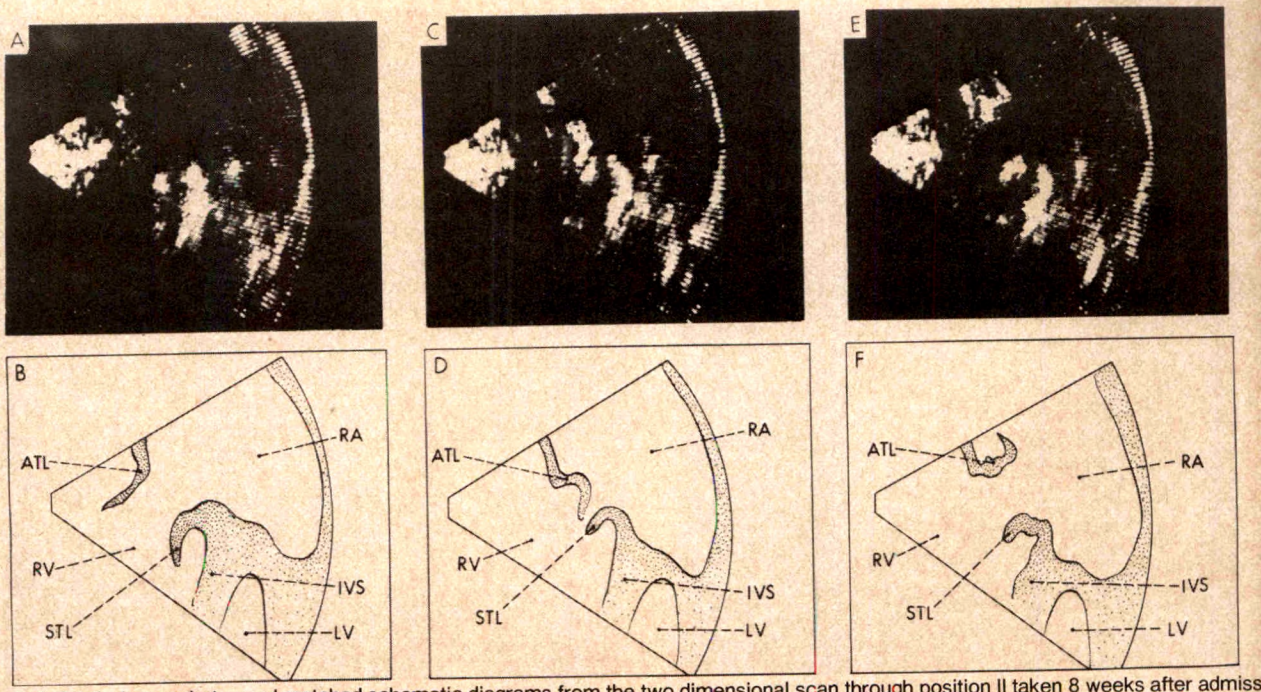


FIGURE 6. Single frame photos and matched schematic diagrams from the two dimensional scan through position II taken 8 weeks after admissio **A** and **B,** the tricuspid valve leaflets open in diastole. **C** and **D,** early systolic prolapse of the anterior tricuspid leaflet. **E** and **F,** mid to late systol flail of the anterior tricuspid leaflet. Abbreviations as in Figure 2.

The left-sided structures visualized in the images in Figures 4 and 6 were thought to represent the posterior portions of the mitral ring and left ventricle near the insertion of the atrial septum. Multiple factors, including cardiac chamber enlargement and chest wall configuration, prevented simultaneous visualization of tricuspid and mitral structures in this patient.

Cardiac catheterization at this time demonstrated a high membranous ventricular septal defect with a pulmonary to systemic flow ratio of 1.6:1. The pulmonary arterial pressure was 31/15 mm Hg and the right atrial pressure data were *a* wave 14, *v* wave 26 and mean 16 mm Hg. Except for disclosure of the ventricular septal defect, the left ventricular angiogram was normal. Biplane right ventricular cineangiography revealed massive tricuspid insufficiency. A radiolucent mass was observed in the pulmonary outflow tract during diastole and was thought to represent the tricuspid leaflet seen in a similar position in the two dimensional echocardiogram.

Closure of the ventricular septal defect and replacement of the tricuspid valve with a porcine prosthesis was performed. At operation, the attachment of the anteriorly positioned tricuspid leaflet was noted to be completely destroyed. The patient had an uncomplicated postoperative course and was discharged on the 9th postoperative day.

Follow-up M mode echocardiography 3 months postoperatively (Fig. 7) revealed normal left ventricular size and septal wall motion. A vibrating structure could be seen within the right ventricular cavity adjacent to the ventricular septum. With two dimensional echocardiography this structure was localized in an area compatible with the residual portion of partially excised papillary muscle to the tricuspid valve.

Discussion

This report demonstrates the value of M mode and two dimensional echocardiography in accurately detecting the serial destructive changes in a tricuspid valve damaged by infective endocarditis. Although standard time-motion echocardiography has been of value in the noninvasive detection of several disorders of the tricuspid valve, to our knowledge, this is the first reported application of the technique to a clinical case of vegetative endocarditis involving the tricuspid valve.[4–9]

Unique to this report, the tomographic images provided by the phased array two dimensional echocardiographic system furnished specific spatial anatomic information concerning the serial changes seen in the infected tricuspid valve. Vegetative involvement and thickening of the anterior tricuspid leaflet with prolapse (Fig. 4) could be seen to progress to a frankly flail leaflet (Fig. 6) over a period of weeks. The relentless destruction detected by this method was also evident in the progressive dilatation of the inferior vena cava that suggested an increased degree of tricuspid incompetence. Nevertheless, the patient's clinical condition improved, with resolution of the various complicating features of his illness and control of the acute infective process. Thus, serial M mode and two dimensional echocardiographic findings called attention to the localized destructive effects of the infection that could not be appreciated on the basis of physical findings alone.

Angiography versus echocardiography: Although the cineangiogram of the right ventricle readily demonstrated tricuspid insufficiency and a flail mass in the pulmonary outflow tract during diastole, the specific details of tricuspid valve anatomy were obscured by the dense simultaneous opacification of both the right atrium and ventricle. Thus, although cardiac catheterization and cineangiography permitted assessment of the patient's hemodynamic state and the severity of the tricuspid insufficiency, the flail nature of the tricuspid leaflet was more fully appreciated with two dimensional echocardiography. The latter technique also permitted serial observations to be made of the progressive destruction of the tricuspid valve.

M mode versus two dimensional echocardiography: M mode and two dimensional echocardiography

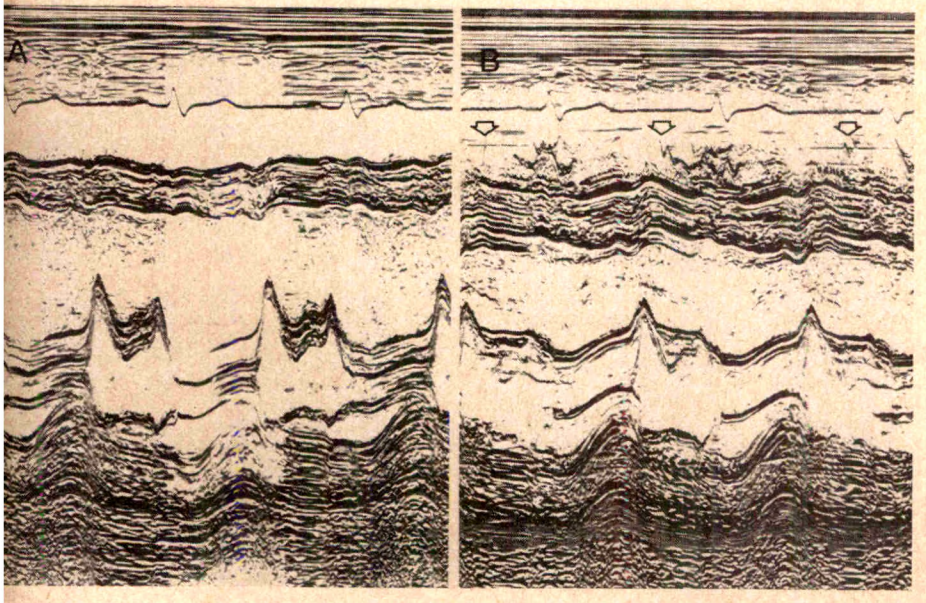


FIGURE 7. M mode echocardiograms taken postoperatively. **A,** left ventricle and mitral valve. **B,** slight medial angulation of the transducer detected an abnormal structure within the right ventricular cavity **(arrows).** A two dimensional scan later showed it to be a portion of a partially excised papillary muscle.

provide anatomic information in two different ways, each with specific clinical utility. In our study, the abnormal tricuspid valve motion was identified with both methods. M mode echocardiography has the unique advantage of recording dynamic motion of target structures in a continuous time fashion. Thus, the graphic display of the rapid oscillations of the diseased tricuspid valve seen in Figures 3 and 5 suggested the presence of a vegetative lesion or disruption of leaflet integrity, or both. Because two-dimensional echocardiography provided no time-related display record, it was difficult to appreciate such subtle vibrations in target movement with this technique. On the other hand, it provided spatial anatomic information that was specific in characterizing the nature of the disordered valve anatomy. Thus, the methods complement each other and neither should be relied upon as the sole source of echocardiographic information.

Time-motion echocardiography, two dimensional echocardiography, cardiac catheterization and cardiac cineangiography all proved useful in providing anatomic or functional information concerning the affected tricuspid valve and, taken together, developed a complete clinical profile of the patient's disordered tricuspid valve function. The high resolution tomographic images provided by real time, two dimensional echocardiography, and its noninvasive methodology, demonstrate the unique quality of this new ultrasonic imaging system to provide important serial information regarding clinical problems.

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Pathologic Correlations in Three Cases of Bilateral Bundle Branch Disease With Unusual Electrophysiologic Manifestations in Two Cases

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Examination of the conduction system in three patients with bifascicular block who had electrophysiologic studies forms the basis for this report. Patients 1 and 2 had left bundle branch block and Patient 3 right bundle branch block and left axis deviation. The H-V interval was prolonged in each case (70, 65 and 60 msec, respectively). Serial section examination of the conduction system revealed sclerodegenerative involvement of both bundle branches in all cases. In Case 1, atrial extrastimulus testing converted left to right bundle branch block; in Case 2, it delineated a sinus echo zone with repetitive sinus nodal reentrance. In the latter case serial section revealed extensive amyloid infiltration of the approaches to the sinoatrial (S-A) node and the atrial preferential pathways. In Case 3, with right bundle branch block and left axis deviation, serial section revealed greater involvement of the anterior part of the main left bundle branch than of the posterior portion as well as involvement of the second part of the right bundle branch.

The study revealed excellent correlation between electrophysiologic and pathologic findings in three cases of intraventricular conduction disease and demonstrated an anatomic basis for the electrophysiologic findings resembling alternating bilateral bundle branch block. Sinus nodal reentrance may be related to disease in the approaches to the S-A node, thereby causing delay in perinodal tissue allowing sinus reentrance. Finally in Case 3, the anatomic substrate for left axis deviation may lie in a greater involvement of the anterior portion than of the posterior portion of the *main* left bundle rather than in the corresponding portions of the periphery.

Previous studies in a limited number of cases from our laboratories have demonstrated good correlations between sites of conduction disease as predicted from electrophysiologic study and subsequent pathologic studies with serial section of the conduction system.[1–5] In this study, we report three additional cases with intact atrioventricular (A-V) conduction, bundle branch block and H-V prolongation. In each case, serial section of the conduction system confirmed the electrophysiologic diagnosis of trifascicular disease. In addition, two patients had unusual electrophysiologic responses to extrastimulus testing. The pathologic significance of these findings is discussed.

Materials and Methods

Electrophysiologic studies: These were performed in three patients as previously described, using a tripolar electrode catheter percutaneously introduced into a right femoral vein and positioned at the tricuspid valve for His bundle recording. A second electrode catheter was percutaneously introduced into the femoral vein and positioned in the high right atrium and used for atrial stimulation in all three cases and for recording the high right atrial electrogram in one case. Electrocardiographic leads I, II, III and V_1 and intracardiac elec-

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m the Congenital Heart Disease Research and ining Center, Hektoen Institute for Medical search; West Side Veterans Administration spital; the Departments of Pathology, North- stern University Medical School; Pritzker hool of Medicine, University of Chicago; The icago Medical School, University of Health ences; Loyola University, Stritch School of dicine; and the Section of Cardiology, Depart- nt of Medicine and the Department of Pathol- , Abraham Lincoln School of Medicine, Uni- sity of Illinois; and the Departments of Pediat- and Medicine, Rush Medical College, Chicago,
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ddress for reprints: Maurice Lev, MD, 637 S. od St., Chicago, Ill. 60612.

trograms were recorded on a multichannel oscilloscopic photographic recorder (Electronics for Medicine DR-16) at paper speeds of 100 and 200 mm/sec. The electrical stimuli were provided by a digital programmable pulse generator (constructed by M. Bloom, Philadelphia, Pa.).

Conduction intervals were recorded during sinus rhythm. The normal values for our laboratory are as follows: A-H interval 54 to 130 msec and H-V interval 31 to 55 msec.[6] The atria were paced at a rate slightly higher than the sinus rate and then at increasing rates (in steps of 10 beats/min) until 1:1 conduction was lost and second degree A-V block observed. Refractory periods were measured with the atrial extrastimulus technique.[7] The test stimulus (S_2) was introduced in Cases 1 and 2 after every 10th spontaneous sinus beat (A_1). The coupling interval was decreased in increments of 10 msec. Sinus responses (Case 2) were analyzed as previously described by Dhingra et al.[8,9] Electrophysiologic findings in Case 1 have been previously published.[10]

Pathologic studies: In all three cases, the sinoatrial (S-A) node and its approaches were serially sectioned and every 10th section was retained. The A-V node and its approaches, the A-V bundle and the beginning of the bundle branches were serially sectioned and every 10th section was retained in Case 1, and every 5th section in Cases 2 and 3. The remainder of the bundle branches up to the region of the moderator band were serially sectioned and every 10th section was retained in all three cases. In Cases 2 and 3, the preferential atrial pathways were serially sectioned, and in the former every 20th and in the latter every 40th section was retained. In addition, in Case 2 of the roofs of both atria were serially sectioned and every 40th section was retained. In all cases the remainder of the heart was cut into blocks and two sections were taken from each block. Alternate sections were stained with hematoxylin-eosin and Weigert-van Gieson stains in Case 1. In Cases 2 and 3 sections containing the S-A and A-V nodes, the A-V bundle and the beginning of the bundle branches were consecutively stained with hematoxylin-eosin, Weigert-van Gieson and Gomori trichrome stains; all other sections were alternately stained with hematoxylin-eosin and Weigert-van Gieson stains. In this manner 914, 1,244 and 1,422 sections were examined in Cases 1, 2 and 3, respectively. In Case 2, additional sections were stained with methyl violet for metachromasia and with Congo Red, and tested for green birefringence with a polarized microscope to detect amyloid. This general method of studying the conduction system has previously been reported.[11] Findings were controlled by studies of aging that included 25 subjects between 50 and 80 years for study of the S-A node and 17 subjects in this age group for the study of the A-V node, bundle and bundle branches.[12,13]

Report of Cases

Case 1

Clinical summary: The patient, a 51 year old man, was admitted to the West Side Veterans Administration Hospital on December 10, 1972 because of chest pain. He had a history of two previous myocardial infarctions, angina pectoris and left ventricular failure. Diagnostic cardiac catheterization was performed on December 23 and revealed diffuse three vessel obstructive coronary artery disease, left ventricular failure and a hypokinetic left ventricle. Coronary disease was judged inoperable and the patient was thus treated medically. On January 7, 1973 the patient was found dead in bed.

Review of electrocardiograms: The admission electrocardiogram on December 10 revealed atrial fibrillation (mean ventricular rate 100/min) and complete left bundle branch block. Subsequent electrocardiograms revealed sinus rhythm with rates of 50 to 60/minute, first degree A-V block (P-R interval 0.20 to 0.22 msec) and left bundle branch block (Fig. 1).

Electrophysiologic studies: These were performed at the time of diagnostic cardiac catheterization on December 23. Control recordings revealed sinus bradycardia (heart rate 50 beats/min) with intact A-V conduction, a normal A-H interval of 95 msec and a prolonged H-V interval of 70 msec (Fig. 2). Type I block proximal to the His bundle was noted at a paced rate of 130/min. Sinus nodal recovery time at a paced rate of 130/min was 1,440 msec and within normal limits.[6]

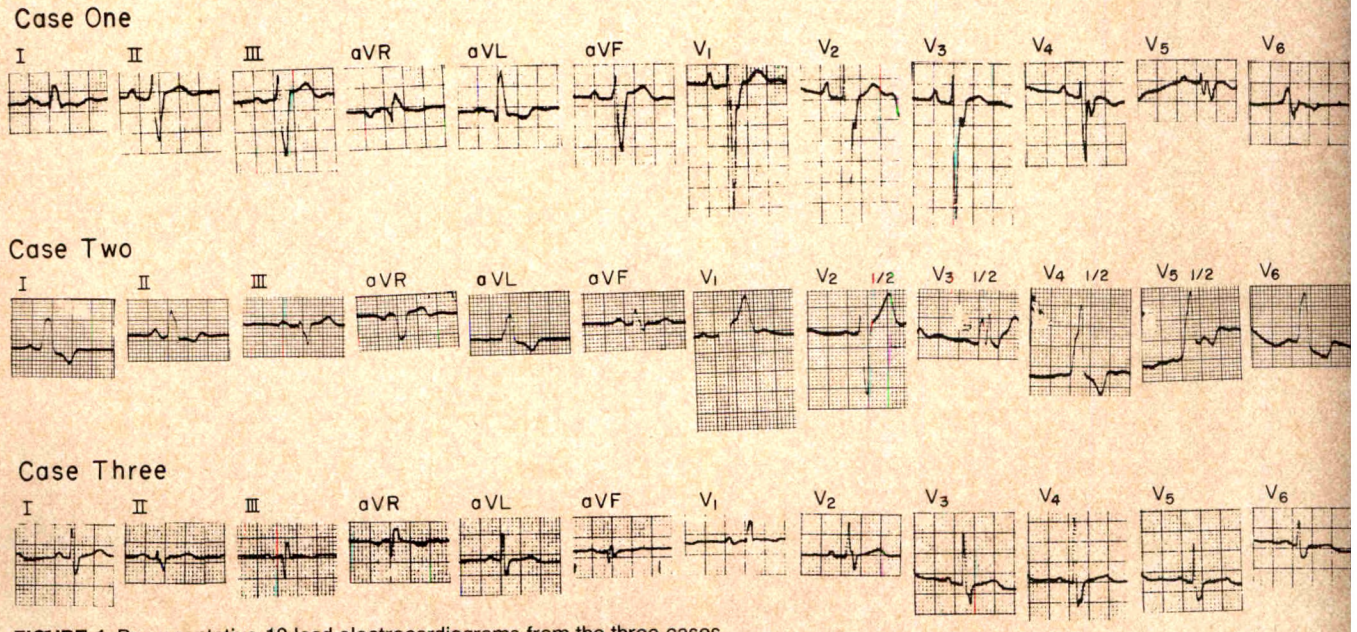


FIGURE 1. Representative 12 lead electrocardiograms from the three cases.

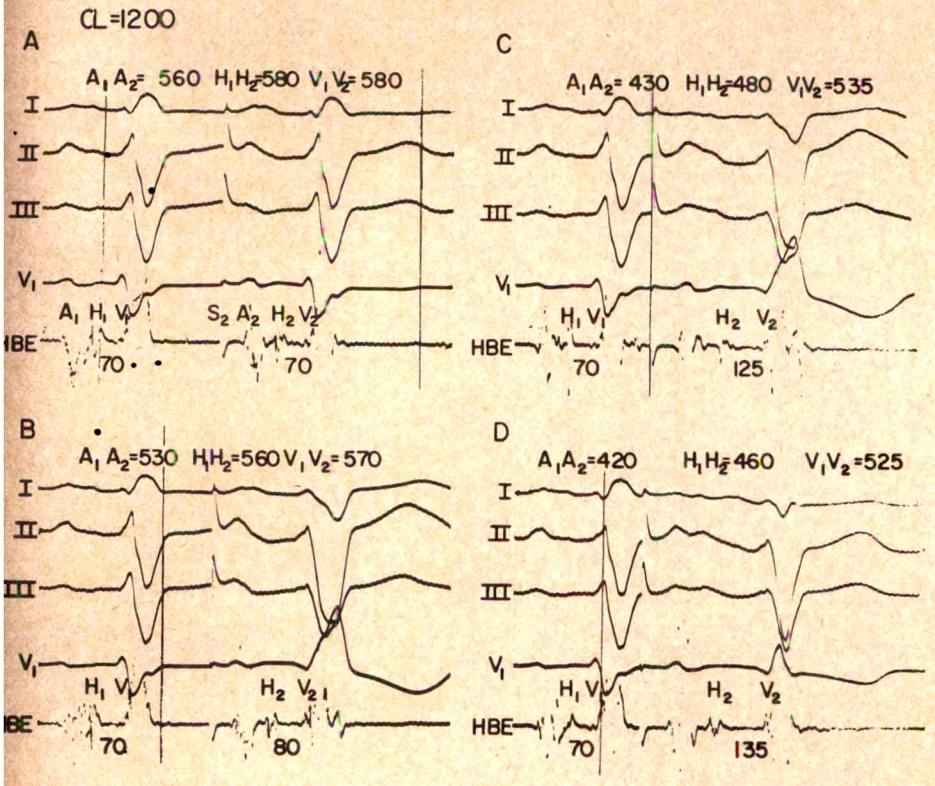


FIGURE 2. Case 1. Conduction intervals and extrastimulus studies. Shown are electrocardiographic leads I, II, III and V_1 and a His bundle electrogram (HBE). A_1, H_1, V_1, S_2, A_2 and V_2 are labeled. A_1-A_2, H_1-H_2 and V_1-V_2 intervals in msec are listed at the top of each panel. H_1-V_1 and H_2-V_2 intervals are listed at the bottom of each panel. Each panel shows the last of 10 sinus beats (cycle length [CL] 1,200 msec) and the extrastimulus and its responses at A_1-A_2 intervals of 560 msec **(A)**, 530 msec **(B)**, 430 msec **(C)** and 420 msec **(D)**. The coupled QRS complex has a pattern of left bundle branch block in **A** and a pattern of right bundle branch block in **B, C** and **D** (see text for discussion). Paper speed 100 mm/sec; time lines at 1 second intervals. (Reprinted from Wu et al.[10])

Atrial extrastimuli were delivered during sinus rhythm. At long coupling intervals, H_2 was conducted with a pattern of complete left bundle branch block (Fig. 2A and 3). As the A_1-A_2 interval was decreased to 530 msec or less with a corresponding H_1-H_2 interval of 560 msec or less, H_2 was conducted to the ventricles with a pattern of right bundle branch block (Fig. 2, B to D and 3). The QRS axis was also shifted leftward (−120°) and the H_2-V_2 interval was lengthened (80 to 125 msec) (Fig 2, B and C). As the A_1-A_2 interval was decreased to 420 msec with a corresponding H_1-H_2 interval of 460 msec, H_2 was conducted to the ventricles with further prolongation of the H_2-V_2 interval to 135 msec with a slightly narrower QRS complex with a pattern of right bundle branch block (Fig. 2D). Conduction was atrial-limited, with normal A-V nodal effective and functional refractory periods (less than 420 and 450 msec, respectively).

Pathologic Findings

Aside from the findings in the heart the only pertinent finding was pulmonary edema.

Heart, gross: The heart was enlarged, weighing 530 g. Hypertrophy and enlargement of all chambers were present. There was severe coronary artery disease and narrowing involving all three major arteries and an organizing and old infarction of the anteroseptal wall.

Conduction system findings: *S-A node:* The S-A node was not available for sectioning.

Approaches to the A-V node: Marked acute degeneration and early necrosis of the cells was present.

A-V node: There was mild elastosis, proliferation of sheath cells and infiltration with mononuclear cells.

A-V bundle: Slight fibrosis was noted.

A-V bundle, branching portion: Moderate to marked fibroelastosis was present.

Left bundle branch: Main bundle: There was partial disruption with fibrosis and space formation at the junction with the A-V bundle (Fig. 4A). This was noted both anteriorly and posteriorly. There was focal eosinophilic degeneration of the remaining fibers, especially marked in the anterior portion.

Periphery: Marked fibrosis was present anteriorly, and moderate fibrosis posteriorly. Moderate vacuolar degeneration was also noted. Some Purkinje cells were small anteriorly.

Right bundle branch: The beginning of the first part showed marked fibrosis accompanied by arteriolosclerosis. Toward the end of the first part, the right bundle branch divided into two parts, and one part showed moderate fibrosis and the other marked fibrosis (Fig. 4B). Eosinophilic degeneration was also seen in the first part. The two parts then joined together in the second part. The second and third parts showed milder similar changes as the first part.

Myocardium: There was marked involvement of the anterior, posterior and septal walls by an old infarct. This was more marked anteroseptally than posteriorly. There was also a recent subendocardial infarct in the anterior wall. Arteriolosclerosis, present throughout the heart, was especially marked in the summit of the ventricular septum. The right ventricle showed scattered small scars. Acute degenerative and early necrotic changes were present in the atria.

Case 2

Clinical summary: The patient, an 83 year old man, was admitted to the University of Illinois Hospital on October 24, 1973 after a syncopal episode. He had a past history of chronic bronchitis and obstructive emphysema, congestive heart failure and urethral stricture. No cause for the syncope was defined, and he was discharged 1 week later. He was then followed up in the conduction disease clinic through March 1974.

He was readmitted to the West Side Veterans Administration Hospital on April 6, 1974 with pneumonia and acute respiratory insufficiency. On April 9 he had a respiratory ar-

rest necessitating intubation and then tracheostomy. From April 9 until his death on May 26, he was treated for recurrent pulmonary infection and respiratory failure.

Review of electrocardiograms: The admission electrocardiogram on October 24, 1973 revealed sinus bradycardia (heart rate 55/min), a P-R interval of 0.16 second and complete left bundle branch block. Subsequent clinical electrocardiograms obtained while he was an outpatient were similar (Fig. 1). The electrocardiogram during his second hospitalization revealed left bundle branch block, episodes of sinus tachycardia, multiple atrial premature beats and occasional ventricular premature beats.

Electrophysiologic studies: These were performed on October 25, 1973 in an attempt to define the mechanism of syncope. Control recordings revealed sinus bradycardia (heart rate 55/min) with intact A-V conduction. The A-H interval was 120 msec and within normal limits. The H-V interval was 65 msec and prolonged (Fig. 5). Wenckebach periods proximal to the His bundle were noted at an atrial paced rate of 140/min. Sinus nodal recovery time at a paced rate of 130/min was 1,350 msec and normal.

Atrial extrastimulus testing was performed during sinus rhythm with A_1-A_2 coupling intervals between 850 and 320 msec. A-V nodal function was within normal limits as defined by an A-V nodal effective refractory period of less than 330

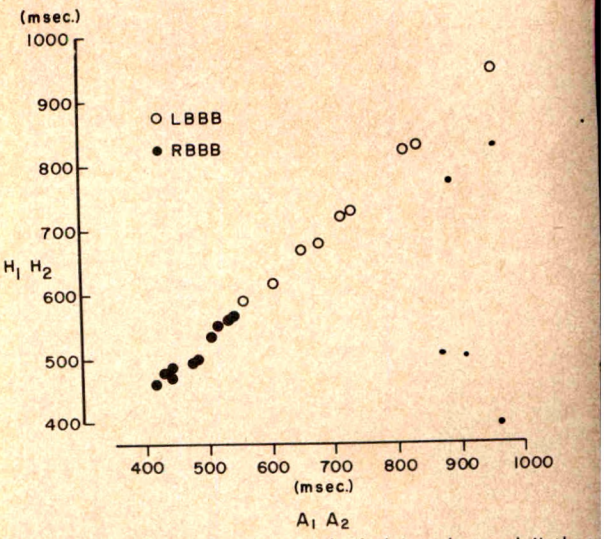


FIGURE 3. Case 1. Conduction curves. A_1-A_2 intervals are plotted on the horizontal axis, and H_1-H_2 intervals on the vertical axis. H_2 responses conducted with a pattern of left bundle branch block (LBBB) are shown as **open circles,** and those conducted with a pattern of right bundle branch block (RBBB) as **closed circles.** There is a well delineated zone in which H_2 is conducted with right bundle branch block.

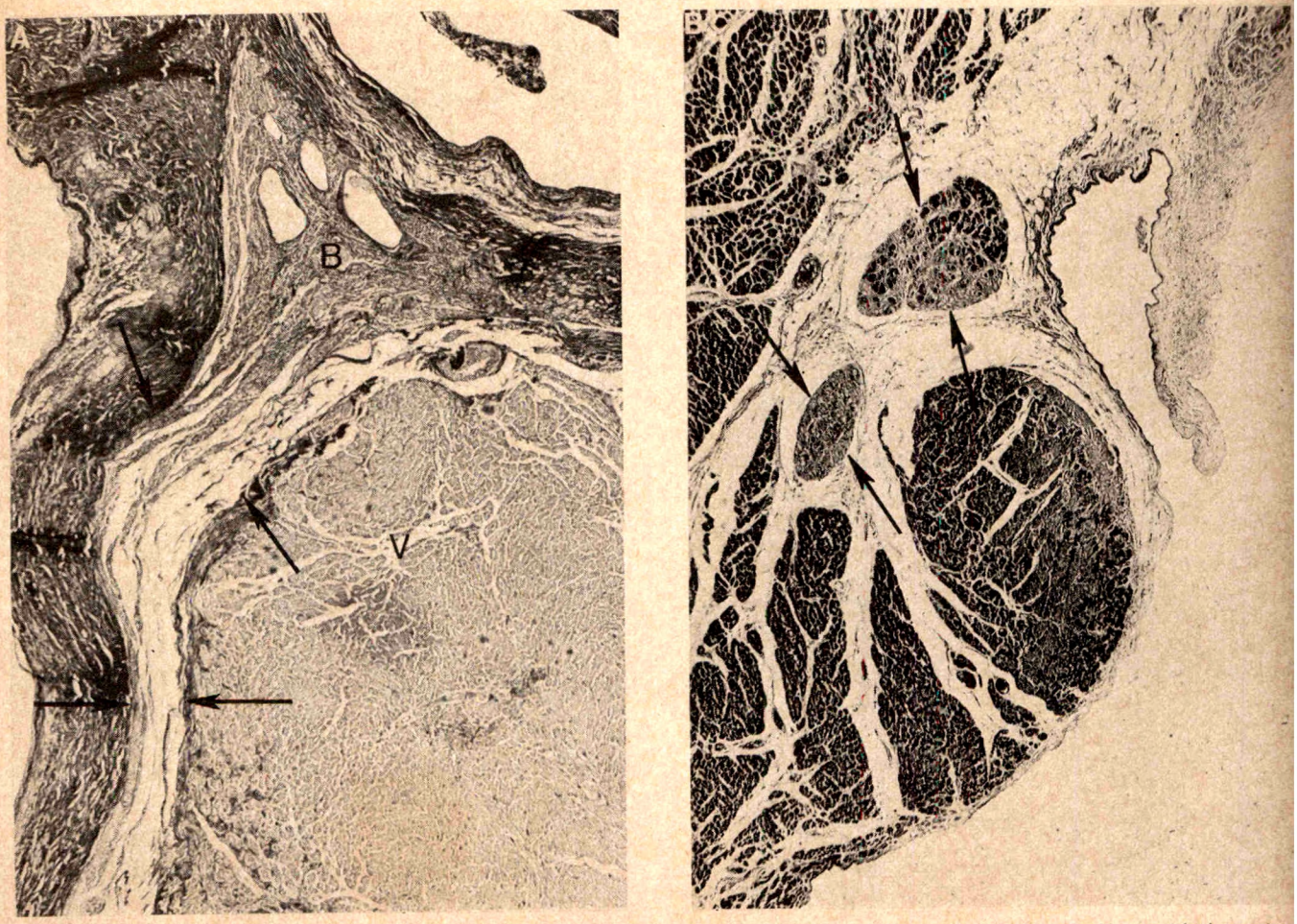
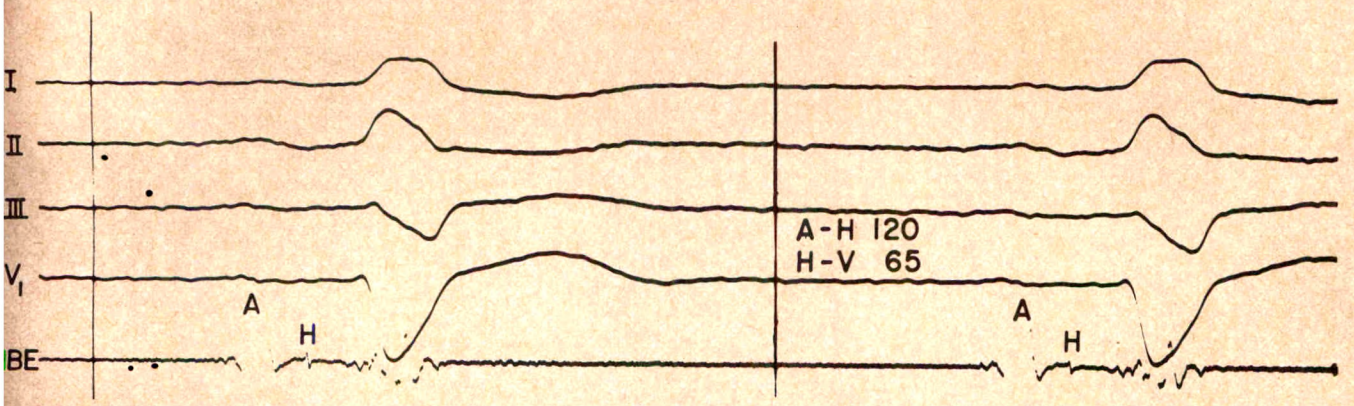
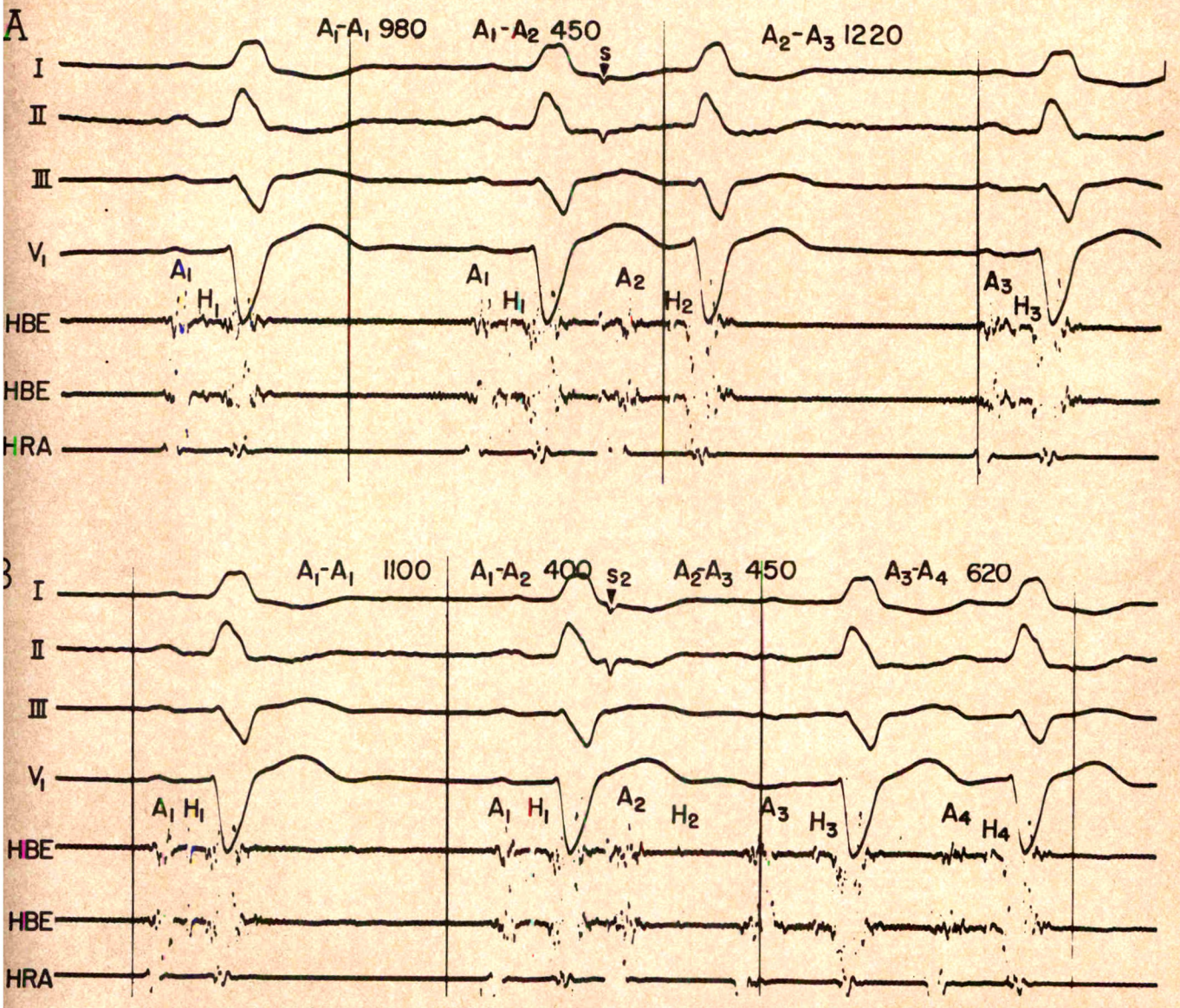


FIGURE 4. Case 1. **A,** partial destruction of the main left bundle branch. **Arrows** point to the left bundle branch. B = A-V bundle; V = ventricular septum **B,** marked fibroelastosis of the end of first part of the right bundle branch. **Arrows** point to the right bundle branch. (Wiegert-van Gieson ×45 [**A** and hematoxylin-eosin ×30 [**B**], both reduced by 25 percent.)



IGURE 5. Case 2. Conduction intervals. Note the pattern of left bundle branch block, the normal A-H interval and the prolonged H-V interval. HBE = His bundle electrogram. Paper speed 200 mm/sec.



IGURE 6. Case 2. Atrial extrastimulus testing. Shown in each panel are two sinus beats followed by an atrial extrastimulus (labeled S) and the ubsequent return cycle or cycles. A high right atrial electrogram (HRA) is recorded on the bottom of each panel. **Panel A** shows a response in ne zone of reset; A_3 is a reset response. **Panel B** shows repetitive sinus echoes; A_3 and A_4 are early responses characterized by a high to low trial activation sequence and a P wave configuration similar to that of the sinus P wave. A_2 (the response to the atrial extrastimulus) is blocked istal to the His bundle (H_2 occurring within the refractory periods of the ventricular specialized conduction system). A_3 and A_4 are both conducted ith a pattern of left bundle branch block. Paper speed 100 mm/sec. HBE = His bundle electrogram.

msec (conduction was atrial-limited) and an A-V nodal functional refractory period of 470 msec. The effective refractory period of the ventricular specialized conduction system was 480 msec, achieved at an A_1-A_2 coupling interval of 420 msec.

Sinus nodal responses were evaluated during extrastimulus testing. A zone of sinus reset[8] was demonstrated between A_1-A_2 coupling intervals of 850 to 410 msec (Fig. 6A). With A_1-A_2 coupling intervals of 400 to 340 msec (the atrial functional refractory period), a sinus echo zone was delineated. Early single and sometimes double echoes (A_3 and sometimes A_4) were noted (Fig. 6B). These were characterized by a high to low atrial activation sequence and a P wave resembling the sinus P wave (Fig. 7B).

Pathologic Findings

Aside from the findings in the heart the important pathologic diagnoses were: (1) bilateral acute and organizing bronchopneumonia, (2) diffuse pulmonary emphysema (bilateral), and (3) acute and chronic bronchitis.

Heart, gross: The heart was slightly enlarged weighing 360 g. There was hypertrophy of the right atrium and ventricle. All three coronary arteries showed marked sclerosis and narrowing. The pars membranacea and the aortic-mitral anulus showed severe calcification.

Conduction system findings: *S-A node:* There was marked amyloid involvement of most small vessels (Fig. 7A).

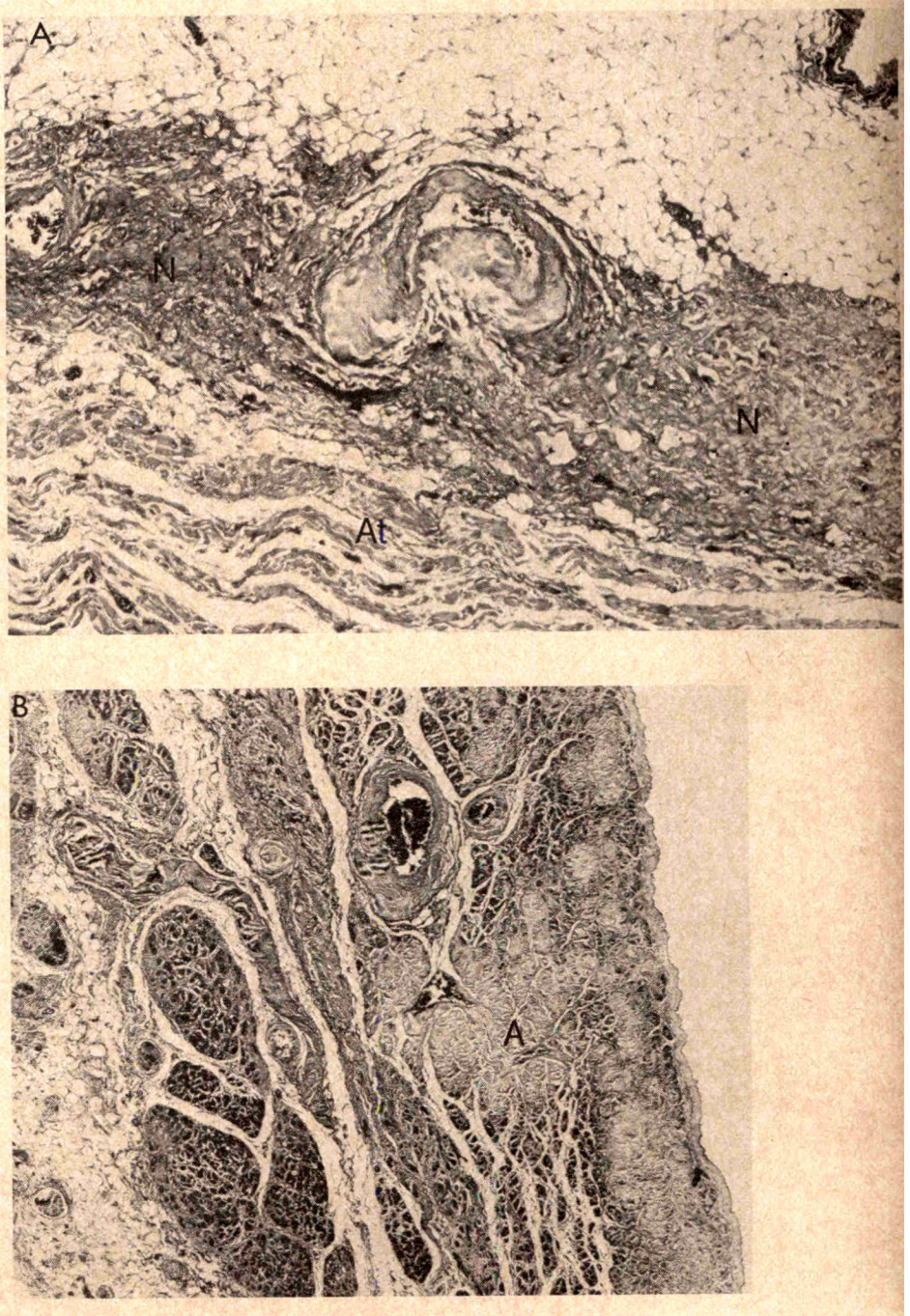


FIGURE 7. Case 2. Amyloid infiltration. **A,** of large arteriole in S-A node (N). **B,** of the approaches to the S-A node. A = amyloid in myocardium; At = atrial musculature. (Weigert-van Gieson ×45 **[A]** and Gomori trichrome ×45 **[B]**, both reduced by 25 percent.)

Approaches to S-A node: Moderate to severe fibroelastosis was present. Amyloid was present in almost all small arteries and in the parenchyma (Fig. 7B). Arteriolosclerosis and chronic pericarditis were noted.

Atrial preferential pathways: Amyloid was present in the parenchyma, both in the muscle and endocardium.

Approaches to A-V node: Amyloid was present in the parenchyma and the vessels.

A-V node: There was severe elastosis and moderate fatty infiltration, mostly in the periphery. Amyloid was present in small vessels.

A-V bundle, penetrating portion: Moderate elastosis was noted, with acute degenerative and early necrotic changes. Calcium pressed on the end of the bundle.

A-V bundle, branching portion: Compression atrophy of the beginning was present (Fig. 8A). This portion was very short.

Left bundle branch: Main bundle: This was disrupted at its junction with the bundle (Fig. 8A). The anterior portion contained a small amount of amyloid. *Periphery:* There was moderate fatty infiltration.

Right bundle branch: Acute degeneration and early necrotic changes were present in the first part. The second part was normal. The third part showed moderate to severe fibroelastosis (Fig. 8B).

Myocardium: Amyloid was present in the small arteries and arterioles throughout the heart. The myocardium of the left atrium, ventricular septum, subendocardial portion of the left ventricle and parts of the right ventricle were infiltrated with amyloid. That of the right atrium showed fibrosis.

Central fibrous body and mitral anulus: These showed areas of calcification.

Case 3

Clinical summary: The patient, a 61 year old man, was admitted to the West Side Veterans Administration Hospital on December 3, 1973 with a fractured hip. He had a history of previous hypertension and two cerebrovascular accidents. He was operated upon on December 7, and a hip nail was inserted. During the course of the operation, marked respiratory insufficiency developed. After operation, the patient had progressive respiratory failure and hypotension and died on December 7.

Review of electrocardiogram: The patient had right bundle branch block and left axis deviation dating back to at least 1972 (Fig. 1). The admission tracing on December 3, 1973 revealed sinus tachycardia (heart rate 110/min), a P-R interval of 0.16 second, complete right bundle branch block and left axis deviation (−30°) and frequent premature ventricular contractions.

Electrophysiologic studies: These were performed on December 6 as part of the preoperative evaluation of the need for prophylactic pacing. Control recordings revealed sinus rhythm at rates of 100 to 110/min with intact A-V conduction and occasional premature ventricular contractions. The A-H interval was 80 msec and normal, and the H-V interval was 60 msec and prolonged (Fig. 9). The patient maintained 1:1 A-V conduction up to a paced rate of 200/min. Sinus nodal recovery time was 700 msec at a paced rate of 130/min.

Pathologic Findings

Aside from the findings in the heart, the pathologic diagnoses were: (1) acute cor pulmonale secondary to massive bilateral pulmonary thromboemboli (recent), (2) recent pulmonary infarction, and (3) marked cerebral atherosclerosis with several old cerebral infarctions.

Heart, gross: The heart was enlarged, weighing 438 g, with hypertrophy and enlargement of all the chambers. The coronary arteries showed minimal narrowing. There was an abnormal architecture of the left ventricle, with high origin of the left coronary ostium above the sinus of Valsalva.

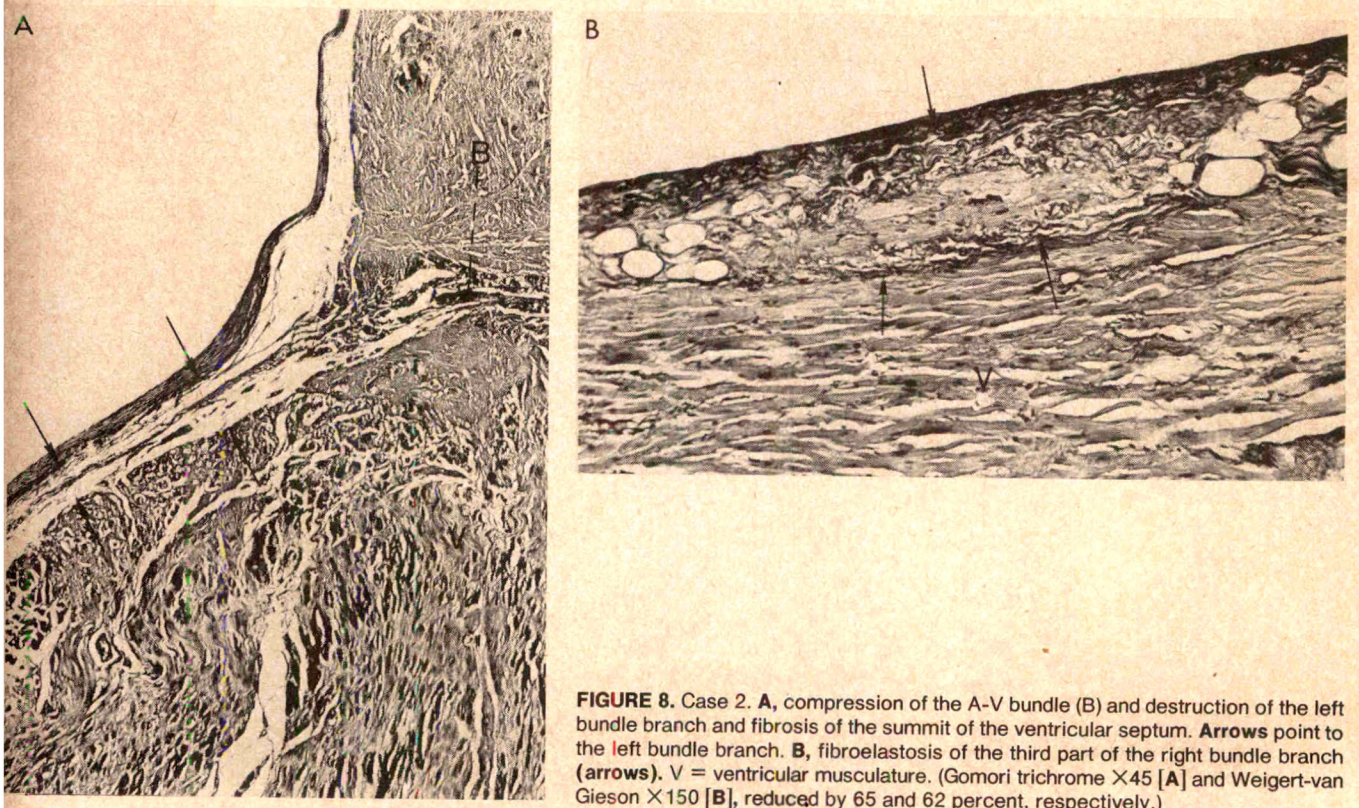


FIGURE 8. Case 2. **A,** compression of the A-V bundle (B) and destruction of the left bundle branch and fibrosis of the summit of the ventricular septum. **Arrows** point to the left bundle branch. **B,** fibroelastosis of the third part of the right bundle branch **(arrows).** V = ventricular musculature. (Gomori trichrome ×45 **[A]** and Weigert-van Gieson ×150 **[B],** reduced by 65 and 62 percent, respectively.)

Conduction system findings: *S-A node:* The ramus ostii cavae superioris was thickened and narrowed just before it entered the node. There was moderate arteriolosclerosis of the node.

Approaches to S-A node: Arteriolosclerosis was marked.

Approaches to the A-V node: The ramus septi fibrosi was markedly thickened and narrowed. There was slight fibrosis of the approaches.

A-V node: Moderate to severe fibroelastosis was present.

A-V bundle, penetrating portion: This was very short and showed no changes.

A-V bundle, branching portion: Moderate fibrosis was present. At its junction with the left bundle branch, it was partially disrupted, with fibroelastic linear formations and spaces. Arteriolosclerosis was moderate.

Bifurcation: There was marked disruption of the left bundle branch at its junction with the bifurcation. The right side showed moderate fibrosis.

Left bundle branch: The posterior part of the main bundle was partially (Fig. 10A) while the anterior was almost completely interrupted (Fig. 10B). The periphery showed slight fatty infiltration.

Right bundle branch: The first part showed moderate fatty infiltration and fibroelastosis. The second part showed marked fibroelastosis (Fig. 10C). The third part was the seat of marked fatty infiltration.

Atrial preferential pathways: There was moderate arteriolosclerosis and sclerosis of the small coronary arteries.

Myocardium: The inferior wall of the left ventricle showed severe fibrosis. This was less severe in the anterior wall. Acute degenerative changes were also apparent. The small microscopic arteries and arterioles were moderately narrowed. Arteriolosclerosis was also present in the left atrium. The summit of the ventricular septum showed severe fibrosis and arteriolosclerosis. This was less apparent further down in the septum.

Discussion

If one considers the intraventricular conduction system as trifascicular (Rosenbaum et al.),[14] all three of our patients had electrocardiographic bifascicular block. The first two had left bundle branch block, implying either predivisional block in the left bundle branch system, or postdivisional block in the two divisions of the left bundle; the third had right bundle branch block with left axis deviation (left anterior hemiblock).

Significance of H-V prolongation: The H-V interval is the interval from the onset of the His bundle electrogram to the onset of ventricular activation as measured from the beginning of the QRS complex in the surface electrocardiogram. In patients with bifascicular block, the H-V interval is a measure of conduction time in the distal His bundle and the remaining functioning fascicle. H-V prolongation in the presence of chronic bifascicular block therefore implies the presence of trifascicular conduction disease. The clinical significance of H-V prolongation in chronic bifascicular block remains controversial. Theoretically, H-V prolongation should imply a high risk of future heart block. Although some workers have reported data supporting this hypothesis,[15,16] prospective studies from our own laboratory have not demonstrated a high risk of heart block in patients with chronic bifascicular block and H-V prolongation.[17–19]

Our three patients all had bifascicular block with H-V prolongation, implying trifascicular conduction disease. The pathologic findings confirmed these electrophysiologic findings, as they have in previous cases.[3,5] In all three cases both bundle branches showed severe, incomplete lesions pathologically, involving the left bundle branch at its origin in all and the first part of the right bundle branch in Case 1, the third part in Case 2 and the second part in Case 3. It is also possible that the disease in the branching portion of the bundle in all three cases contributed to the electrophysiologic findings. The etiologic types of involvement were of two kinds. In Case 1, the pathologic changes were clearly due to coronary disease, in Case 3 to sclerosis of the left side of the cardiac skeleton, and in Case 2 to a combination of these factors.

Alternating bundle branch block: In Case 1 a pattern of right bundle branch block was superimposed within a critical range of H_1-H_2 coupling intervals. The ability to conduct with right bundle branch block in this case strongly implied that the left bundle branch block was incomplete despite the electrocardiographic indication that it was complete.[10] If it had been complete then superimposition of functional right bundle branch block with coupled pacing would have resulted in block distal to the His bundle recording site. The ability to conduct with a pattern of right bundle branch block implied functional integrity of the left bundle branch system. These electrophysiologic findings resemble

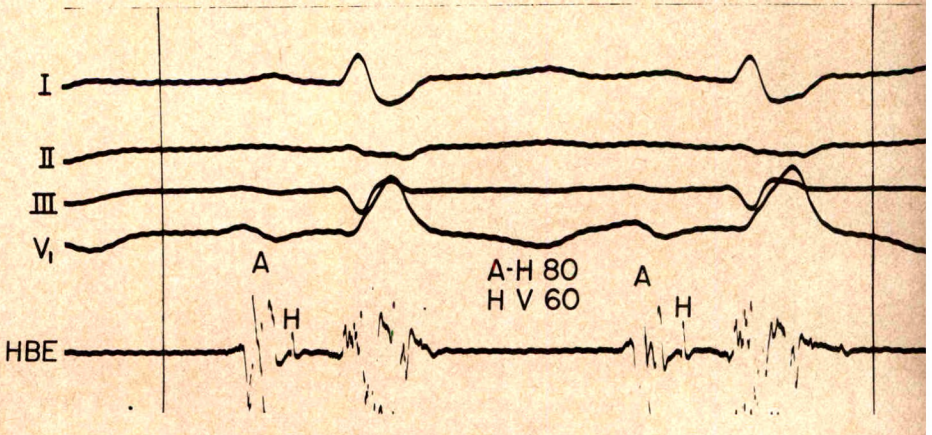


FIGURE 9. Case 3. Conduction intervals. Note the normal A-H interval of 80 msec and the prolonged H-V interval of 60 msec. Paper speed 100 mm/sec. HBE = His bundle electrogram.

those found in some patients with alternating bundle branch block, in whom we have demonstrated incomplete block of one bundle branch and rate-dependent bundle branch block of the contralateral bundle.[20] The clinical significance of such a pattern of conduction would seem to be that of having bundle branch block with a prolonged H-V interval.[20] The pathologic counterpart in Case 1 (that is, the partial involvement of both bundle branches) corresponds to previous findings by Unger et al.[21] and Lenègre[22] in "masquerading" or alternating bundle branch block.

Sinus echoes and sinus nodal reentry: The sinus echo zone in Case 2 was of interest. With use of atrial extrastimulus testing in the animal laboratory, sinus

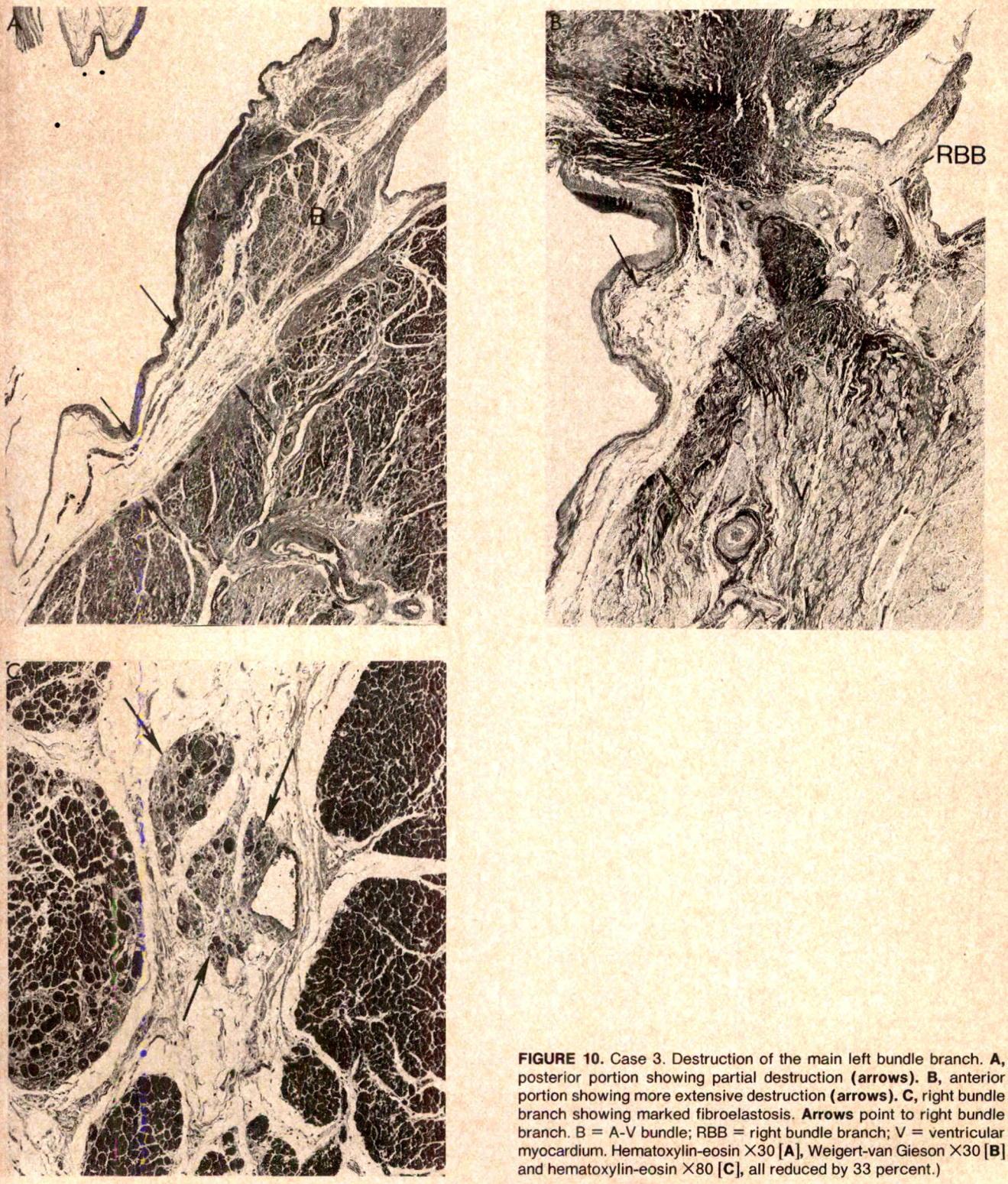


FIGURE 10. Case 3. Destruction of the main left bundle branch. **A,** posterior portion showing partial destruction **(arrows). B,** anterior portion showing more extensive destruction **(arrows). C,** right bundle branch showing marked fibroelastosis. **Arrows** point to right bundle branch. B = A-V bundle; RBB = right bundle branch; V = ventricular myocardium. Hematoxylin-eosin ×30 **[A],** Weigert-van Gieson ×30 **[B]** and hematoxylin-eosin ×80 **[C],** all reduced by 33 percent.)

echo zones can frequently be demonstrated.[23–27] The sinus echo phenomenon in these experiments is believed to reflect the presence of slow conduction with unidirectional block in perinodal tissues, predisposing to reentrance. Crushing of the area of the sinus node eliminates these zones.[25] In contrast, sinus echo zones in man are infrequent. We recently reported[8] sinus nodal responses to atrial extrastimulus testing in 36 patients without apparent sinus node disease. Of these, only four (11 percent) manifested sinus echoes at close coupling intervals. The sinus echoes in Case 2 appeared to differ somewhat from the echo zones described in our previous study. The echo zone in Case 2 was of longer absolute duration, occurred at relatively later coupling intervals and was characterized frequently by the occurrence of double responses (A_3 and A_4) as opposed to the single responses in our earlier study.[8] The potential for double responses suggests some similarity to patients with sustained sinus nodal reentrant paroxysmal supraventricular tachycardia, a group of patients in whom atrial disease is usually found.[28] The patient in Case 2 had documented episodes of sinus tachycardia during his last hospital admission, but it was impossible with the available electrocardiographic data to determine whether these were paroxysmal sinus reentrant tachycardias or nonparoxysmal sinus tachycardia related to respiratory insufficiency.

The pathologic findings in Case 2 define a basis for sinus nodal reentrance. The presence of amyloid in the approaches to the S-A node and in the atria in general, in addition to the severe fibrosis, is probably related to the sinus echo phenomena, sinus bradycardia and, possibly, to episodes of sinus tachycardia. The presence of amyloid in the approaches to the A-V node apparently did not affect A-V nodal function in Case 2. This may be related to the extensive area of the A-V nodal approaches and hence the difficulty of obliterating its function. The A-V node has also marked autonomic innervation that may play a major role in A-V nodal function.

Pathologic basis for left anterior hemiblock: In Case 3, in which there was right bundle branch block with left axis deviation, the anterior part of the main left bundle branch was more involved than the posterior, whereas there were no remarkable changes in the periphery of this bundle. In two previous cases of right bundle branch block with left axis deviation we found the posterior part of the main left bundle more involved than the anterior.[3]

Similar inconsistencies have been reported by others. Thus Demoulin and Kulbertus[29] found equal involvement of the posterior and anterior fibers in anterior fascicular block in 5 cases while five others showed more involvement of the anterior. In a more recent piece of work, in a study of 8 cases of left anterior fascicular block, these authors[30] found that the fibrosis appeared to be evenly distributed in four and predominantly in the anterior and midseptal fibers in four. Fernandez et al.[31] found more changes in the anterior than in the posterior fibers of the left bundle branch in anterior fascicular block. Blondeau and Lenègre[32] in cases of right bundle branch block and left anterior fascicular block found that the involvement of the left bundle branch was not necessarily anterior but in some cases medially and posterior as well as anterior. Also, Sugiura et al.[33] in right bundle branch block and left axis deviation found generalized involvement of the main left bundle branch as well as the intermediate zone in most cases. And Entman et al.[34] in partial block or left axis deviation found no specific portion of the conduction system involved. Thus from our cases and those reported previously, we may conclude that a morphologic basis for left anterior fascicular block has not yet been defined. However, our Case 3 suggests that it is possible for left axis deviation to occur as a result of involvement of the anterior portion of the left *main* bundle branch rather than of the anterior peripheral fasciculi.

Acknowledgment

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Quinidine-Induced Ventricular Flutter and Fibrillation Without Digitalis Therapy

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Three cases are described with documented ventricular flutter and fibrillation during quinidine medication without concomitant digitalis therapy. In all three patients the arrhythmia developed while they were receiving moderate doses of quinidine. Although no changes in QRS width were observed after administration of quinidine, there was marked prolongation of the Q-T interval. The mechanism of development of ventricular flutter and fibrillation in patients taking quinidine may be similar to that in patients with the Q-T prolongation syndrome.

Adverse reactions to quinidine are well known. Among them quinidine-associated syncope has been poorly understood. Recording the electrical activity of the heart during such syncope has shown that a paroxysmal, usually self-terminating, episode of ventricular flutter and fibrillation is probably responsible.[1–21] We describe herein three patients with documented ventricular fibrillation and flutter, not receiving digitalis, whose arrhythmia was attributed to the administration of quinidine alone.

Case Reports

Case 1

A 31 year old woman complained for several years of short episodes of a rapid heart action accompanied by slight dizziness. These episodes had increased in frequency and duration over the years. During one episode she was admitted to another hospital on May 4, 1974, and an electrocardiogram showed an atrioventricular (A-V) junctional tachycardia with a ventricular rate of 200/min. Routine blood chemistry and electrolyte values were normal.

On admission, the patient received verapamil (Isoptin®), 10 mg intravenously, which resulted in return of a normal sinus rhythm. An intravenous infusion of verapamil (15 mg over 8 hours) was started, as well as treatment with quinidine sulfate (1,200 mg daily by mouth). On the morning of May 6 she had a seizure that terminated spontaneously within 1 minute. No electrocardiogram was obtained during this episode. On the afternoon of the same day another seizure occurred; the electrocardiogram now showed ventricular fibrillation. Defibrillation was carried out and she was given one injection of diphenylhydantoin (125 mg intravenously). Thereafter she was transferred to our hospital. At that moment the blood quinidine level was 6.7 mg/liter. In the ambulance and after admission she had several episodes of ventricular fibrillation (Fig. 1). Only one episode required electrical termination. All medication was withheld and within 12 hours no more episodes of ventricular arrhythmias were observed.

Case 2

A 63 year old woman had short episodes of vertigo without loss of consciousness over a 10 year period. During several examinations occasional premature ventricular contractions were registered. During an exercise test a short episode of ventricular tachycardia was recorded, during which she remained asymptomatic. She was admitted to another hospital where treatment with quinidine bisulfate (Kinidine Durettes®), 500 mg twice daily, was started on April 10, 1974. On April 12 she suddenly lost consciousness for a few minutes. She awoke spontaneously and several short runs of ventricular tachycardia were recorded.

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She was transferred to our hospital. Physical examination revealed no abnormalities. Results of routine blood analysis, including electrolyte determinations, were normal.

The electrocardiogram revealed sinus rhythm with frequent unifocal premature ventricular beats, many in runs of two and three; these were frequently interrupted by runs of ventricular flutter lasting 10 to 30 seconds (Fig. 2A). These episodes usually terminated spontaneously but occasionally required electrical defibrillation. The dose of quinidine was increased to 500 mg three times daily; thereafter the episodes of ventricular flutter increased, frequently occurring at a rate of three to five times in 5 minutes. An intravenous bolus injection of 100 mg of lidocaine was given, followed by a lidocaine drip infusion at 3 mg/min, but there was no improvement. Administration of quinidine and lidocaine was stopped, and procainamide hydrochloride (Pronestyl®) was given in a dose of 500 mg intravenously and 500 mg orally, followed by 250 mg intravenously every 30 minutes for 2 hours. During this period there was a further increase in the episodes of ventricular flutter. Over a period of 2 hours the patient had about 100 episodes of ventricular flutter and underwent defibrillation 35 times. Administration of procainamide was then discontinued and bretylium tosylate, 300 mg, was given intramuscularly, which resulted in prompt disappearance of the arrhythmia. Finally, oral administration of diphenylhydantoin, 100 mg three times daily, combined with alprenolol, 400

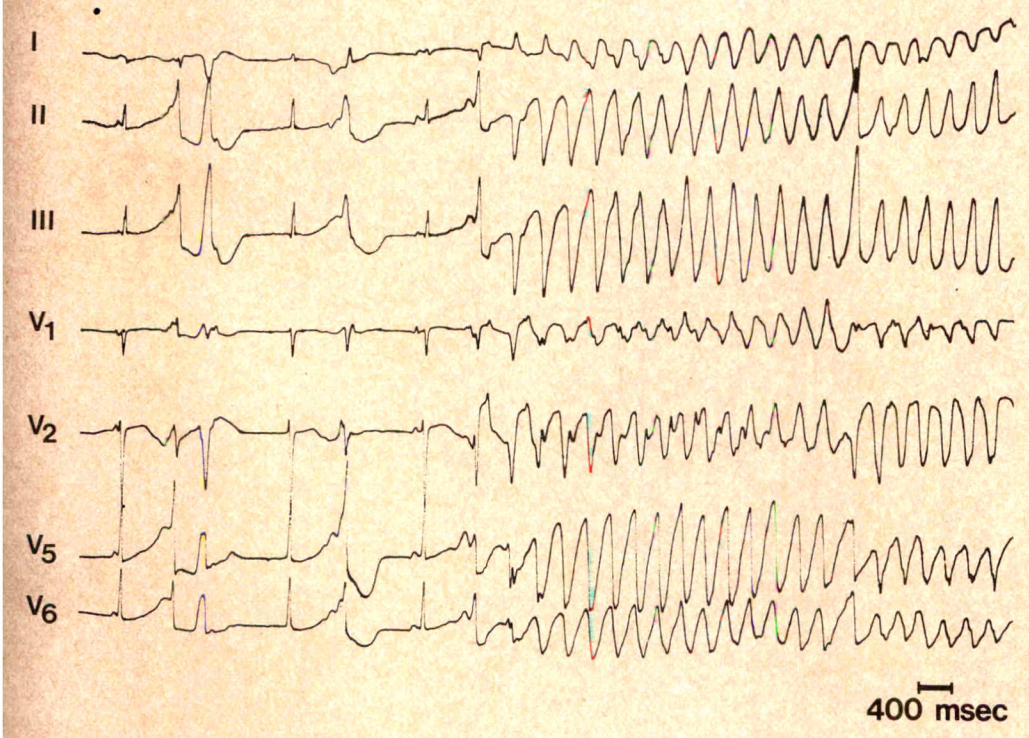


FIGURE 1. Case 1. Initiation of ventricular fibrillation. All leads were recorded simultaneously. Note the marked Q-T prolongation after the narrow supraventricular QRS complexes.

fig. 2a

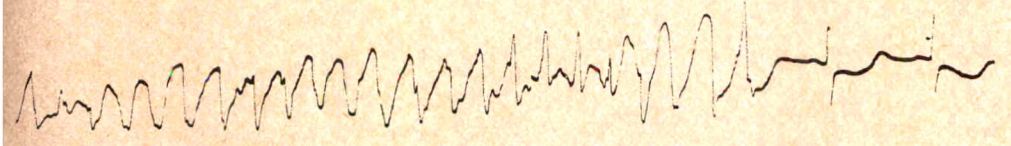


fig. 2b

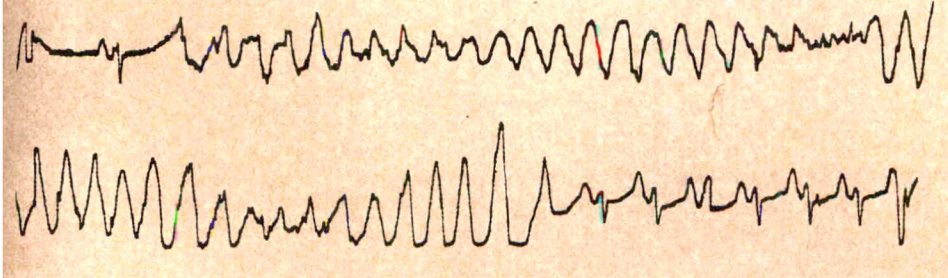


FIGURE 2. a, Case 2. Monitor lead showing spontaneous termination of the ventricular tachyarrhythmia. **b,** Case 3. Monitor lead showing initiation and spontaneous termination of chaotic ventricular rhythm. The registration is continuous.

mg twice daily, abolished and prevented all ventricular irritability.

Case 3

A 29 year old woman underwent mitral commissurotomy in 1967 because of mitral stenosis with mild aortic incompetence. In 1972 she had atrial fibrillation with a high ventricular rate; after treatment with digitalis, normal sinus rhythm returned. Administration of digitalis was discontinued on August 28, 1972, and treatment with quinidine bisulfate, 500 mg three times daily, was started on the same day. She was discharged the next day with normal sinus rhythm. During the night of September 7, in which she experienced several episodes of rapid heartbeat, accompanied several times by loss of consciousness and seizures, she was admitted to our department.

On physical examination there were the characteristic auscultatory findings of mitral stenosis and aortic incompetence. Results of routine laboratory blood analysis, including serum electrolyte determinations, were normal. The electrocardiogram revealed sinus rhythm with ventricular bigeminy, occasionally interrupted by short periods of ventricular flutter and fibrillation, that were recognized by the patient and her husband as the fainting spells of that night (Fig. 2B). Administration of quinidine was discontinued, and the attacks did not recur.

Discussion

A striking point of similarity in our three patients was marked prolongation of the Q-T interval after only a moderate dose of quinidine. The phenomenon was completely reversible 7, 4 and 4 days, respectively, after discontinuation of the drug (Table I, Fig. 3). Cheng et al.[22] have noted problems in measuring the Q-T interval in the presence of prominent U waves. The latter were evident only in Case 1; even taking into account the precautions suggested by Cheng et al., the "true" Q-T interval was prolonged by 15 percent in this case.

In Case 1, verapamil was administered in addition to quinidine. Although this drug's mode of action is not completely understood, recent reports[23,24] suggest that its antiarrhythmic properties cannot be attributed to prolongation of ventricular depolarization and repolarization. However, our data do not exclude the possibility that ventricular fibrillation in Case 1 was partly or completely due to concomitant administration of verapamil.

TABLE I

Relation Between Administration of Quinidine, QRS Duration (sec) and Corrected Q-T Interval ($Q\text{-}T_c$) (sec) in Three Cases

	Before Quinidine Treatment		During Quinidine Treatment			After Discontinuation of Quinidine	
Case no.	QRS Duration	$Q\text{-}T_c$	Dose (g/24 hr)	QRS Duration	$Q\text{-}T_c$	QRS Duration	$Q\text{-}T_c$
1	0.06	0.44	0.8	0.08	0.64	0.08	0.44
2	0.08	0.42	0.8	0.08	0.72	0.08	0.41
3	0.08	0.39	1.2	0.08	0.66	0.09	0.38

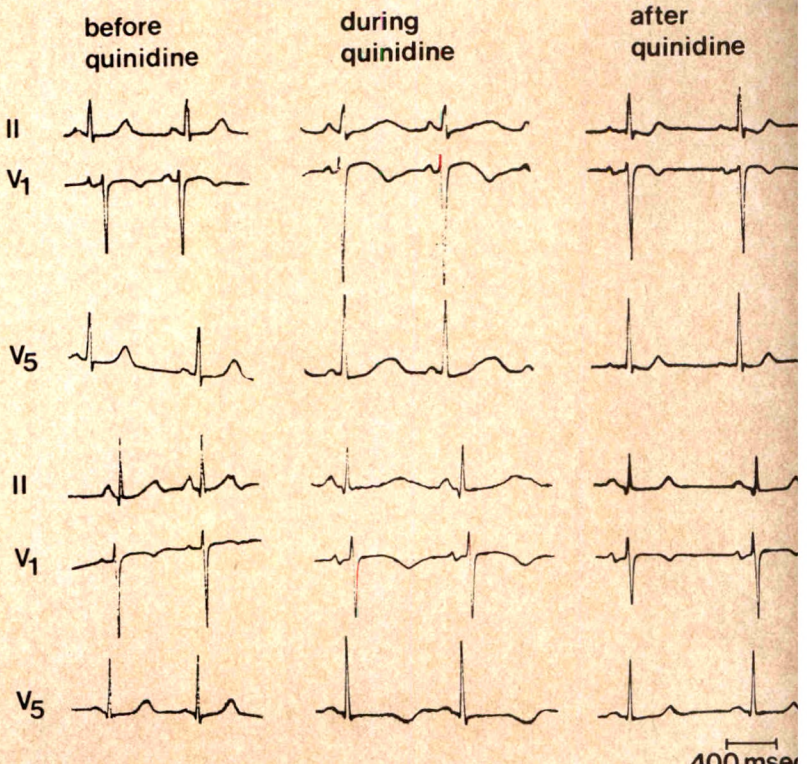


FIGURE 3. Three selected leads (II, V_1 and V_5) from Case 1 **(upper half of figure)** and Case 2 **(lower half)** before, during and 7 (Case 1) and 4 days (Case 2) after discontinuation of administration of quinidine. There are changes in the Q-T interval during administration of quinidine without changes in the width of the QRS complex.

In Case 2, the episodes of ventricular flutter and fibrillation increased in frequency after an increase in the dose of quinidine, and especially after administration of procainamide, but the prolonged Q-T interval had been noted before administration of the latter drug. Because the electrophysiologic properties of procainamide and quinidine are similar, it is not surprising that the drugs have a similar clinical effect in the susceptible patient.

Mechanism of quinidine-induced ventricular fibrillation: The effects of quinidine on the electrical activity of cardiac cells have recently been reviewed by Hoffman et al.[25] Whereas true quinidine intoxication is usually accompanied by prolongation of the duration of the QRS complex, this did not occur in our patients (Table I). As long ago as 1929 Davis and Sprague[1] realized the importance of differences in conduction velocity and speed of recovery in ventricular muscle as factors in the mechanism of initiation of ventricular fibrillation. They also suggested that quinidine and digitalis, used in combination, might facilitate the occurrence of this arrhythmia.

Table II lists reported cases in which syncope occurring after administration of quinidine was proved to be induced by ventricular flutter or fibrillation. There have been other reports of the occurrence during administration of quinidine of rhythm and conduction disturbances, such as ventricular tachycardia or complete atrioventricular (A-V) block, which in itself may lead to syncope, ventricular fibrillation or sudden death.[26] Therefore Table II includes only those cases in which a clear electrocardiographic or monitor observation of ventricular flutter or fibrillation during a syncopal attack was not preceded by another major arrhythmia.

Table II demonstrates that in almost all cases digitalis was given concomitantly with quinidine or withheld only a short time earlier. We are not aware of electrophysiologic studies documenting dangerous effects of this combination of drugs although increased incidence of ventricular fibrillation has been reported in the dog heart when procainamide and digitalis are administered together.[27]

Quinidine-associated syncope and Q-T prolongation syndrome: Q-T prolongation, in the absence of QRS widening during quinidine-associated syncope, has previously been noted.[7,10,17,21] One might speculate that the ventricular tachyarrhythmias during quinidine-associated syncope have the same electrophysiologic basis as ventricular fibrillation occurring in the "Q-T prolongation syndrome."[28–32] It may be that patients showing inappropriate lengthening of the Q-T interval after administration of quinidine have a "forme fruste" of the Q-T prolongation syndrome. Our observations suggest that in patients receiving quinidine one should monitor closely not only QRS width but also the length of the Q-T interval. Further work is needed to determine whether the degree of Q-T prolongation will be of value in identifying patients who may have ventricular tachyarrhythmias after administration of quinidine.

Treatment: If ventricular tachyarrhythmias develop after administration of quinidine, the drug should be withheld immediately. As demonstrated in our Case 2, drugs with similar pharmacologic effects, such as procainamide, ajmaline and disopyramide, should not be given. In Case 2 the arrhythmia was controlled by combining a beta blocking agent with diphenylhydantoin. This combination of drugs has also been successful in controlling ventricular tachyarrhythmias in patients with the Q-T prolongation syndrome.[30,32] The administration of lidocaine both by intravenous bolus injection and infusion was not helpful in our Case 2. This finding is contrary to the experience of Kaplinski et al.[21] and in agreement with that of Lyon et al.[20]

One may conclude that in patients showing a prolonged Q-T interval and in patients reacting to quinidine and similar drugs with a disproportionate prolongation of the Q-T interval, quinidine and related drugs should be considered contraindicated. The possible aggravating effect of concomitant administration of digitalis deserves further study.

TABLE II

Reported Cases of Documented Ventricular Flutter (VFL) or Fibrillation Associated With Quinidine Therapy

References	Cases: Total Reported	Cases: no. With Digitalis Administration	Cases: Q-T Prolongation Noted	Remarks
Davis and Sprague[1]	1	1	...	Digitalis discontinued 4 days before VFL
Acierno and Gubner[2]	1	1	...	Digitalis intoxication
Efrati[3]	2	2	...	Improvement with procainamide in 1 case
Rainier-Pope et al.[4]	2	2	...	...
Rokseth and Storstein[5]	1	1	...	...
Bellet[6]	1	...	...	...
Selzer and Wray[7]	6	6	1	...
Davies et al.[8]	1	1	...	...
Brenner et al.[9]	1	?	...	...
Rubeiz et al.[10]	1	1	1	...
Rothfeld et al.[11]	1	1	...	...
Bloem and Büthker[12]	2	2	...	...
Paul[13]	1	?	...	Digitalis not mentioned but probable
Seaton[14]	1	1	...	...
Latour et al.[15]	2	1	...	...
Stein and Schollmeyer[16]	1	1	...	...
Bjerkelund and Skålland[17]	2	2	2	...
Oravetz and Slodki[18]	1	1	...	...
de Neeling[19]	1	...	...	...
Lyon et al.[20]	1	...	...	No improvement with lidocaine
Kaplinski et al.[21]	1	1	1	Improvement with lidocaine
Total	31	25	...	...

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Mustard Operation and Creation of Ventricular Septal Defect In Two Patients With Transposition of the Great Arteries, Intact Ventricular Septum and Pulmonary Vascular Disease

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The condition of patients with transposition of the great arteries, intact ventricular septum and severe pulmonary vascular disease is inoperable with present techniques. In a series of 260 surgically treated patients with transposition of the great arteries and intact ventricular septum, 5 had severely increased pulmonary vascular resistance, and all 5 died; postmortem examination confirmed the presence of severe pulmonary vascular disease. The concept of the "palliative Mustard" procedure was applied in two children with transposition of the great arteries, intact ventricular septum and pulmonary vascular disease who underwent the Mustard operation with creation of a ventricular septal defect. The postoperative course was uneventful in both patients. Thirteen and 5 months, respectively, after operation, both are physically active and have respective arterial oxygen saturation levels of 94 and 92 percent.

The fate of patients with transposition of the great arteries, ventricular septal defect and pulmonary vascular disease has been improved by the concept of a "palliative Mustard" operation.[1] Correction of inflow by the Mustard technique is carried out, but the ventricular septal defect is left open. This defect provides the necessary vent should the pulmonary vascular resistance increase. Although the long-term prognosis of patients after the palliative Mustard operation remains unknown, the procedure increases the systemic oxygen saturation resulting in a subsequent increase in exercise tolerance and improvement in general condition.

We recently treated two cyanotic severely disabled children who had transposition of the great arteries with an atrial septal defect, intact ventricular septum and pulmonary vascular disease. We performed a Mustard operation and created a ventricular septal defect in the apical portion of the muscular septum. The surgical technique and immediate results form the basis of this report. This approach may provide useful palliation for patients with transposition of the great arteries, intact ventricular septum and severe pulmonary vascular disease.

Case Reports

Case 1

The patient was a 5 year old girl, born on June 16, 1969 after a full-term pregnancy and normal delivery, weighing 3.4 kg at birth. A cardiac murmur was heard at age 3 months and she became cyanotic at age 6 months. Transposition of the great arteries and pulmonary atresia was diagnosed clinically. Because the cyanosis was increasing and exercise tolerance diminished, she was admitted for investigation to another hospital at age 3 years. Cardiac catheterization at that time established a diagnosis of transposition of the great arteries, intact ventricular septum and atrial septal defect. Over the next 2 years her condition gradually deteriorated so that at age 5 years the possibility of Mustard's oper-

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ation was considered. At this stage, she was referred to our unit for operation. On admission in April 1974, she could walk only a few meters. She also had repeated lower respiratory infections.

On examination, severe cyanosis and marked clubbing were evident. The chest was deformed as a result of a bulging sternum and marked bilateral rib depression. The cardiac rhythm was regular, the peripheral pulses were all readily palpable and the pulse character was normal. The central venous pressure was not increased, but the liver was palpable 1 cm below the right costal margin. The precordial impulse was marked and suggested enlargement of the heart, together with hypertrophy of the left ventricle. A systolic thrill was present, without radiation to the neck. The first heart sound was normal, the second single and loud; a third sound of moderate intensity was also present. A full length systolic murmur was audible over the whole precordium, maximal at the left sternal edge; there was no diastolic murmur. Examination was otherwise normal. Her weight at this time was 15.2 kg and height 110 cm. The hemoglobin was 13.2 g/100 ml.

The chest roentgenogram revealed marked cardiac enlargement. The proximal pulmonary vessels were prominent. The electrocardiogram confirmed sinus rhythm although the P-R interval (0.20 second) was prolonged for the heart rate (150/min). There was moderate biventricular hypertrophy.

The essential findings at cardiac catheterization are shown in Table I. The pulmonary arteriolar resistance was greatly elevated at 14 units m^2. There was no shunt at the ventricular level.

The angiocardiogram confirmed the diagnosis of transposition of the great arteries with intact ventricular septum. The aneurysmal dilatation of the main pulmonary artery (Fig. 1) in the absence of pulmonary valve stenosis may be interpreted as the probable result of progressive pulmonary hypertension. A lung biopsy was considered but not undertaken because cardiac catheterization and angiocardiography confirmed the severe elevation of the pulmonary arteriolar resistance. The child's condition was considered inoperable by standard techniques, but palliation with the Mustard operation and the creation of a ventricular septal defect seemed a logical alternative.

Preoperatively the child's hemoglobin was 13.2 g/100 ml. This finding, in the presence of an arterial oxygen saturation of 46 percent and an arterial partial pressure of oxygen of 34 mm Hg, suggested a relative anemia. It was decided not to treat this anemia before operation.

At operation (July 1, 1975) the heart was approached through a midline sternotomy. There was a left juxtaposition of the atrial appendages and a small left superior vena cava draining into the coronary sinus. The main pulmonary artery was grossly enlarged and was compressing the right superior vena cava. The aorta, which was to the left of the pulmonary artery, was cannulated with a right-angled metal cannula. Rygg cannulas were placed directly into the right superior vena cava and inferior vena cava. The left superior vena cava was temporarily occluded.

With the patient on cardiopulmonary bypass and under moderate hypothermia (25°C), the right atrium was opened. A large atrial septal defect and the ostia of both atrial appendages were visualized. The remnant of the atrial septum was excised and the raw area was covered with interrupted stitches. The coronary sinus was cut back and a trouser-shaped pericardial patch was inserted in the usual manner. The ostia of both atrial appendages were left behind the baffle, that is, on the systemic venous side. An apical left ventriculotomy was then performed, and the lowest part of the muscular septum was excised. The excision was performed from the left side with a finger placed through the tricuspid valve into the right ventricle to guide the excision and to prevent damage to the papillary muscle. A defect of approximately 2 cm in diameter was created. It admitted a no. 20 Hegar dilator on the beating heart. The left ventricle was then closed and the interatrial baffle completed. The cavity of the pulmonary venous atrium was very small. This is a constant finding in patients with transposition of the great arteries and juxtaposition of the atrial appendages.[2] The atriotomy was therefore extended between the right upper and right lower pulmonary veins and a gusset of woven Dacron® was inserted to enlarge the posterior and lateral walls of this cavity. The patient was then rewarmed and perfusion was discontinued without difficulty. The heart took over in sinus rhythm, the blood pressure was 90/60 mm Hg and the PO_2 88 mm Hg with an inspired oxygen concentration of 50 percent.

TABLE I

Case 1. Cardiac Catheterization Data

	Oxygen Saturation (%)	Pressure (mm Hg)
Superior vena cava	38	. . .
Inferior vena cava	38	. . .
Right atrium	64	(8)
Right ventricle	45	90/12
Aorta	46	85/60 (70)
Pulmonary vein	98	. . .
Left atrium	83	(8)
Left ventricle	85	90/10
Pulmonary artery	74	90/50 (65)

Height	110 cm
Weight	15.2 kg
Hemoglobin	13.2 g/100 ml
Body surface area	0.7 m^2
Assumed oxygen consumption	126 ml/min
Pulmonary blood flow	4.05 liters/min per m^2
Pulmonary arteriolar resistance	14 units m^2

Figures in parentheses indicate mean pressure.

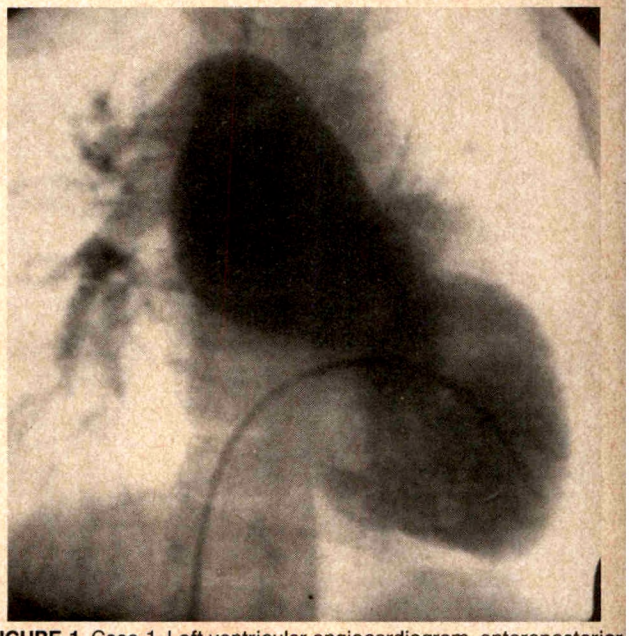


FIGURE 1. Case 1. Left ventricular angiocardiogram, anteroposterior projection. The pulmonary artery arises directly from this ventricle and is grossly dilated. There is no valvular or subvalvular obstruction.

TABLE II

Case 2. Cardiac Catheterization Data

	Oxygen Saturation (%)	Pressure (mm Hg)
Superior vena cava	45	...
Inferior vena cava	47	...
Right atrium	54	(4)
Right ventricle	45	120/10
Aorta	44	105/70 (85)
Pulmonary vein	96	...
Left atrium	86	(6)
Left ventricle	82	110/2
Pulmonary artery	85	105/65 (80)

Height	106 cm
Weight	15.5 kg
Hemoglobin	23.5 g/100 ml
Body surface area	0.68 m^2
Assumed oxygen consumption	102 ml/min
Pulmonary blood flow	3.75 liters/min per m^2
Pulmonary arteriolar resistance	20 units m^2

Figures in parentheses indicate mean pressures.

The patient was intubated with a nasotracheal tube and was ventilated on the Engström ventilator for the next 3 days. She went home 11 days after the operation, on a regimen of digoxin, furosemide and potassium chloride. Her color was pink and she had an arterial oxygen saturation of 93 percent.

On reexamination 10 months after operation a similar but less pronounced murmur without thrill was still audible. An additional murmur of rough quality heard over the scapula, and not present preoperatively, has been attributed to the created ventricular septal defect. The second heart sound has remained single and loud. It presumably represents the aortic component, the pulmonary component not being heard on the surface of the chest; this is a frequent finding in transposition of the great arteries, whatever the associated defects. Arterial PO_2 was 71 mm Hg and arterial oxygen saturation 94 percent during breathing of room air. The child was active and able to walk 2 miles.

Case 2

The patient was a 5 year old girl, born June 6, 1970 after a full-term pregnancy and normal delivery. Cyanosis and failure to thrive were noted at age 2 weeks. Cardiac catheterization, performed at age 1 year, established the diagnosis of transposition of the great arteries, atrial septal defect and intact ventricular septum. Subsequent follow-up appointments were not kept, and the patient was not seen until age 4 years. At that time, she had severe cyanosis and clubbing. The hemoglobin was 19.4 g/100 ml. She was referred for further investigation and treatment to our unit.

On examination, she had cyanosis with clubbing of fingers and toes. There were no signs of heart failure. The pulse was 96/min and regular; no murmurs were audible. The second heart sound was loud and single; only the pulmonary component was heard. The chest roentgenogram revealed severe cardiomegaly with marked enlargement of the pulmonary vessels in the right hilar region. The electrocardiogram disclosed sinus rhythm and right ventricular hypertrophy.

The findings at cardiac catheterization are shown in Table II. The pulmonary arteriolar resistance was greatly elevated at 20 units m^2. Right ventricular angiocardiography confirmed the diagnosis of transposition of the great arteries and intact ventricular septum.

Operation was performed on September 19, 1975. Before institution of cardiopulmonary bypass, a biopsy specimen was taken from the right lower pulmonary lobe. During bypass, a pericardial baffle was inserted in the usual fashion. A ventricular septal defect was then created in the apical part of the ventricular septum using the same technique as described in Case 1. Perfusion was then discontinued without difficulty. The patient was ventilated on the Engström ventilator for 2 days. She continued to have sinus rhythm. The lung biopsy specimen revealed grade III pulmonary vascular obstructive disease.

The postoperative course was uneventful and she was discharged on the 12th postoperative day. The hemoglobin was 13 g/100 ml, hematocrit 39 percent, arterial PO_2 68 mm Hg and arterial oxygen saturation 92 percent. She was taking digoxin, 0.1 mg twice daily. Five months later, her color was reported to be pink and she had improved exercise tolerance.

Discussion

Pulmonary vascular disease develops early in patients with transposition of the great arteries and ventricular septal defect.[3,4] The prognosis of patients with transposition of the great arteries, ventricular septal defect and patent foramen ovale has been much improved as a result of Lindesmith's concept of the palliative Mustard procedure. Patients have only an atrial baffle inserted but the ventricular septal defect is not closed. Their color becomes pink, and their exercise tolerance increases.[5,6]

Although much less common, pulmonary vascular disease does occur in patients with transposition of the great arteries and intact ventricular septum.[3,7,8] In our series of 260 Mustard operations for transposition with intact ventricular septum, only five patients had severe hypertension with a high pulmonary vascular resistance. All five died during or soon after the operation. Because the Mustard operation is generally considered contraindicated in patients with a high pulmonary vascular resistance, the reported results of the palliative Mustard operation for transposition of the great arteries and ventricular septal defect[1,6] and our own experience with this operation encouraged us to offer a similar procedure to children who had transposition with an intact ventricular septum and pulmonary vascular disease.

We created the ventricular septal defect at the apex for fear of inducing atrioventricular block by resecting the upper part of the interventricular septum. To our knowledge, attempts to create a high ventricular septal defect in order to perform Rastelli's operation in patients with tranposition of the great arteries and left ventricular outflow tract obstruction have not been successful.[9]

Our immediate results were encouraging. The color of each patient became pink, and the arterial oxygen saturation level increased from 45 to 94 and from 44 to 92 percent, respectively. The exercise tolerance of both patients greatly increased.

The long-term prognosis of the patient with transposition and severe pulmonary vascular obstructive disease is uncertain. However, previous reports have substantiated the significant relief from symptoms and improvement in exercise tolerance that the palliative Mustard operation provides. The approach described herein makes this relief available to the patient with transposition and an intact ventricular septum.

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Cardiac Involvement in the Kugelberg-Welander Syndrome

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Two cases of the Kugelberg-Welander syndrome (juvenile form of progressive spinal muscular atrophy) associated with cardiomyopathy and cardiomegaly are presented. The first patient, a 24 year old man, had atrial flutter with complete atrioventricular (A-V) block due to A-H block. Echocardiography revealed an increase in the left atrial and right ventricular dimensions. The second patient was a 26 year old man whose electrocardiogram revealed an A-V junctional rhythm, deep Q wave in leads I, aVL and V_5 to V_6 and an RS pattern in lead V_1. Histologic examination of the myocardium in Case 2 showed slight interstitial fibrosis. Review of previously reported cases shows that (1) the atrium, the ventricular myocardium and A-V conducting tissue may be involved, and (2) atrial arrhythmias, A-V conduction disturbances and congestive heart failure may occur in the Kugelberg-Welander syndrome.

Among heredofamilial degenerative neuromuscular diseases, Friedreich's ataxia,[1] myotonic dystrophy[2,3] and Duchenne's muscular dystrophy[4,5] are very often associated with cardiomyopathy. The heart has also been reported to be involved in other neuromuscular diseases including the Roussy-Lévy syndrome,[6] familial spastic paraplegia,[7] the cerebellar form of spinocerebellar degeneration,[8] peroneal muscular atrophy,[9] spinal scapuloperoneal muscular atrophy,[10] limb-girdle muscular dystrophy,[5] facioscapulohumeral muscular dystrophy,[5] distal myopathy,[11] ocular myopathy[12] and scapuloperoneal dystrophy.[13] Study of the cardiomyopathy associated with these diseases is of importance, not only from the standpoint of clinical practice but also from the standpoint of contributing to the etiology of idiopathic cardiomyopathy, especially regarding genetic factors in the development of familial cardiomyopathy.

The Kugelberg-Welander syndrome is a juvenile form of progressive spinal muscular atrophy described by Wohlfart et al.[14] and Kugelberg and Welander.[15] The characteristic features are (1) onset in childhood or adolescence, (2) atrophy and weakness of proximal limb muscles followed by involvement of distal muscles, (3) slowly progressive clinical course, (4) occurrence of fasciculation and electromyographic and muscle biopsy evidence of lower motor neuron lesion, and (5) nonsex-linked recessive mode of inheritance. There have been only a few case reports of cardiac changes in this syndrome. In this paper, we present two cases of Kugelberg-Welander syndrome with cardiac involvement.

Methods of Cardiovascular Examination

His bundle electrography: His bundle electrograms were recorded by the method of Scherlag et al.[16] using a no. 6 tripolar probe (Castillo) and a multichannel recorder (rectigraph and visigraph, Sanei Sokki Co., Ltd.) with the frequency response set at 500 hertz and the time constant at 0.003 second. The paper speed was either 100 or 125 mm/sec. Atrial pacing was performed with a second catheter positioned against the lateral wall of the right atrium, using

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a Medtronic 5880 A pacemaker. The P-A, A-H and H-V intervals were measured according to the method of Narula et al.[17]

Echocardiography: Echocardiograms were obtained using a sonolayergraph model SSL-51 H (Toshiba Co., Ltd.) and a 2.0 megahertz transducer with a diameter of 1 cm. They were recorded on a strip chart recorder (model OR-O1A, Toshiba Co., Ltd.). Right ventricular dimension, left ventricular internal dimension, left ventricular and interventricular septal wall thicknesses, left atrial dimension, aortic root and E-F slope and amplitude of the anterior mitral valve leaflet were measured according to the method of Feigenbaum.[18]

Endomyocardial biopsy: Myocardial biopsy was performed using a Konno-Sakakibara endomyocardial bioptome.[19] Histologic sections of the biopsy specimens were stained with hematoxylin-eosin.

Presentation of Cases

Case 1

A 24 year old tailor was admitted to Kagoshima University Hospital because of arrhythmias in October 1974. He seemed normal until age 6 years, when it was noted that he was clumsy in running. Proximal weakness of the arms was noted several years before admission. He was found to have bradycardia at age 19 years but he did not experience syncope or palpitation. Several weeks before his admission, precordial distress developed. One uncle and one cousin were reported to be affected by neurologic disorders.

On admission, he was well developed. The pulse was 44/mi and regular. The blood pressure was 120/60 mm Hg. A grad 2/6 systolic murmur was heard at the cardiac base. A soft an smooth liver was palpable 3 cm below the right costal margin The spleen was not palpable. Neurologic examination dis closed muscular weakness and atrophy in the proximal portio of the arms and both proximal and distal portions of the legs Fasciculations were seen. Only the Achilles tendon reflexe were elicited. The gait was waddling. The sensory examinatio was normal. Pes cavus was noted. The electromyogran showed a neurogenic pattern. Muscle biopsy revealed neuro genic muscular atrophy. The nerve conduction velocity wa 60 m/sec in the left ulnar nerve.

The serum glutamic oxaloacetic transaminase (SGOT) wa 108 units, glutamic pyruvic transaminase (SGPT) was 15 units and creatine phosphokinase (CPK) ranged from 57.5 t 84 units (normal less than 35 units). Measurements of serun cholesterol, beta lipoprotein, triglycerides, electrolytes, protei fractions and blood glucose were all within normal range. Th chest X-ray film revealed moderate cardiomegaly with norma lung fields. The electrocardiogram on admission (Fig. 1) re vealed atrial flutter with complete atrioventricular (A-V block.

A His bundle electrogram (Fig. 2) showed a sharp and di phasic His bundle potential (H) preceding each *V* wave. Th H-V interval was 50 msec. No *A* wave was followed by a Hi bundle potential. The rate of *V* waves was 40/min. Thus it wa demonstrated that the A-V block was due to A-H block.[17] A

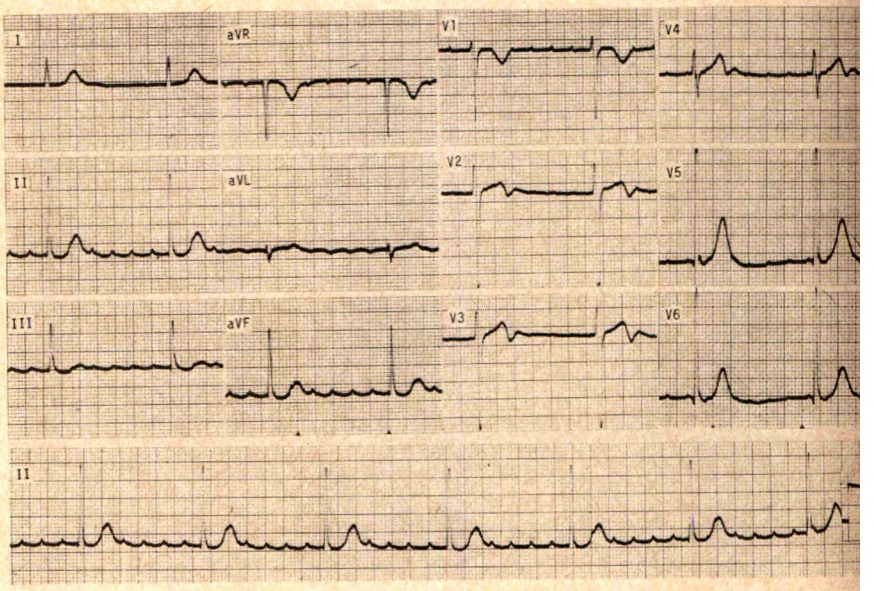


FIGURE 1. Case 1. Electrocardiogram showing atrial flutter with complete A-V block. The R-R intervals are almost regular and measure 1.4 seconds.

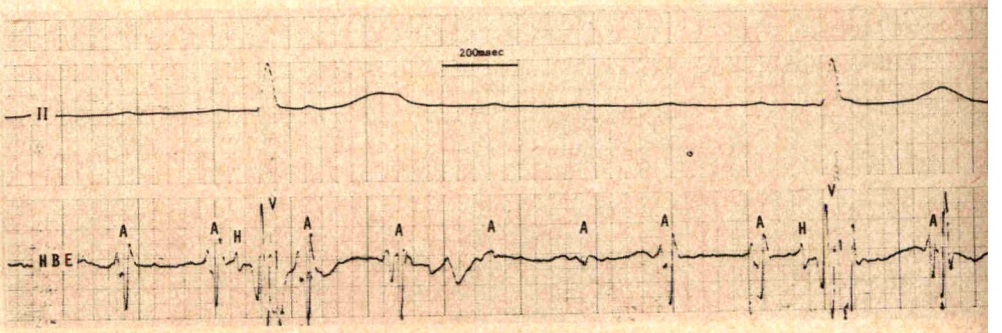


FIGURE 2. Case 1. His bundle electrogram and electrocardiogram (lead II) showing atrial flutter with complete A-V block due to A-H block. The His bundle potential is recorded before each *V* wave. The H-V interval is 50 msec.

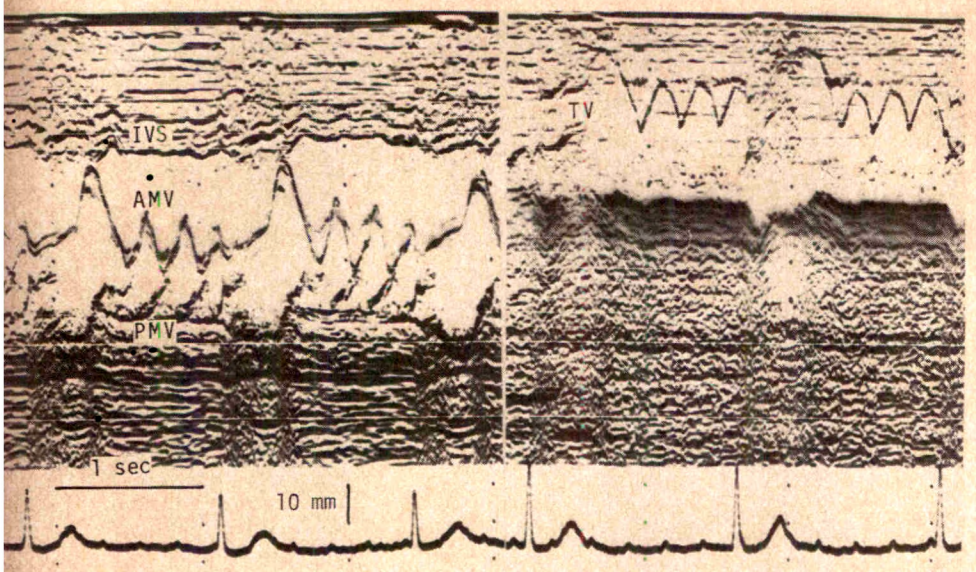


FIGURE 3. Case 1. Echocardiograms. **Left,** an undulatory pattern synchronous with the flutter waves in the electrocardiogram is present in the anterior (AMV) and posterior (PMV) mitral valve leaflets and interventricular septum (IVS). **Right,** tricuspid valve echoes (TV) show the same pattern.

echocardiogram (Fig. 3) showed an undulatory pattern of mitral valve leaflets, tricuspid valve leaflets and interventricular septum. Right ventricular and left atrial dimensions (1.4 and 2.3 cm/m^2, respectively) were increased. The electrocardiogram taken several weeks later revealed sinus bradycardia with complete A-V block. Right heart catheterization revealed normal intracardiac pressures and no intracardiac shunt.

Case 2

A 26 year old man was admitted for further evaluation of heart disease in July 1973. He had had difficulty in running since childhood. At age 16 years he noticed proximal muscular atrophy of the limbs and since then had had slowly progressive difficulty in walking. Three months before admission, he was told that he had cardiomegaly and an abnormal electrocardiogram. He complained of exertional palpitation. An uncle and a cousin were reported to have similar abnormality of the musculature.

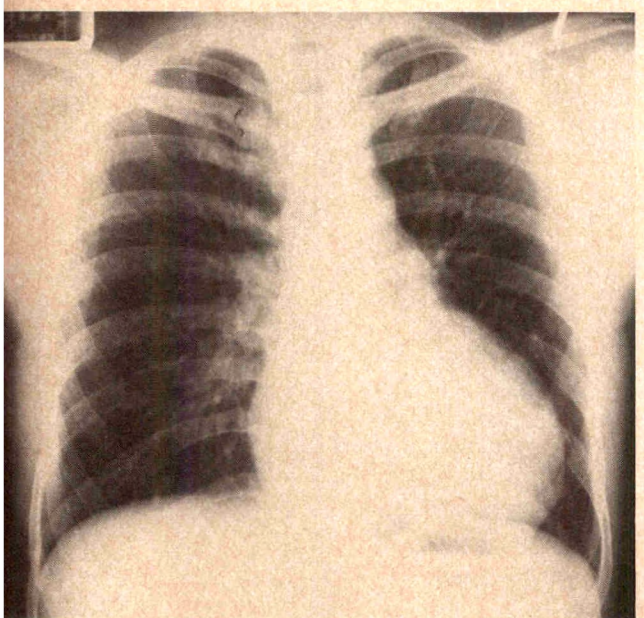


FIGURE 4. Case 2. Chest X-ray film showing cardiomegaly. The cardiothoracic ratio is 0.587.

On admission, he was moderately developed and well nourished. The pulse was 84/min and regular. The blood pressure was 132/84 mm Hg. On auscultation, a grade 2/6 systolic murmur at the apex and a grade 1/6 systolic murmur at the base were audible. Muscular atrophy and weakness of the proximal type were noted. The deep tendon reflexes were normal or slightly diminished. The gait was waddling. The sensation was normal. The electromyogram revealed a mixed neurogenic and myogenic pattern. Muscle biopsy of the right quadriceps femoris muscle revealed mixed neurogenic and myogenic muscular atrophy.

The serum electrolytes, SGOT, SGPT, serum protein fraction and serum cholesterol were all within normal range. The serum CPK ranged from 49.2 to 156.5 units. Serologic tests for syphilis were negative. The chest X-ray film (Fig. 4) showed cardiomegaly. The electrocardiogram (Fig. 5) revealed an A-V junctional rhythm. The mean QRS axis was about 0°. There were deep Q waves in leads I, aVL and V_5 to V_6, and an RS in V_1. Small notches in the QRS complex were seen in leads II, III, aVL and aVF.

His bundle electrograms showed normal values; the P-A interval was 30 msec, the A-H interval 56 msec and the H-V interval 40 msec. The A-V conducting response to atrial pacing was also normal.[20] Right heart catheterization revealed no abnormality. A biopsy specimen obtained from the right ventricle showed a slight interstitial fibrosis.

Discussion

Cardiac involvement: There have been only a few reports of the cardiac changes in the Kugelberg-Welander syndrome (Table I). In 1971, Sterz et al.[21] described two brothers with the Kugelberg-Welander syndrome who had atrial fibrillation. The older brother, aged 35 years, manifested Adams-Stokes syndrome, atrial fibrillation and A-V block with idioventricular rhythm; he was successfully treated with implantation of an artificial cardiac pacemaker. The younger brother

had atrial fibrillation and cardiomegaly. Descriptions of three patients with Kugelberg-Welander disease and cardiomyopathy have appeared in Japanese. Matsumoto et al.[22] described a 23 year old man with this disease in 1971. The patient had cardiomegaly, ascites, hepatomegaly and edema. The electrocardiogram revealed atrial standstill and low voltage of the QRS complexes. Sugimura et al.[23] described two other patients with this disease. The first was a 23 year old woman who complained of exertional palpitation. The electrocardiogram revealed first degree A-V block, atrial premature beats and paroxysmal atrial tachycardia. His bundle electrograms revealed prolongation of the A-H interval. Fibrosis of the right atrium was demonstrated by endomyocardial biopsy. The second patient, a 31 year old man, had dyspnea. The electrocardiogram showed transient atrial fibrillation, atrial premature beats, left axis deviation and T waves suggesting coronary disease. Patient 1 in our study had precordial distress, cardiomegaly and atrial flutter with complete A-V block due to A-H block; Patient 2 had exertional dyspnea, cardiomegaly, A-V junctional rhythm and abnormal Q waves. Thus, among seven patients with symptomatic heart disease, atrial arrhythmias were found in six, cardiac conduction disturbances in four, cardiomegaly in five and frank heart failure in two.

The atrial arrhythmias frequently found in patients with the Kugelberg-Welander syndrome may indicate

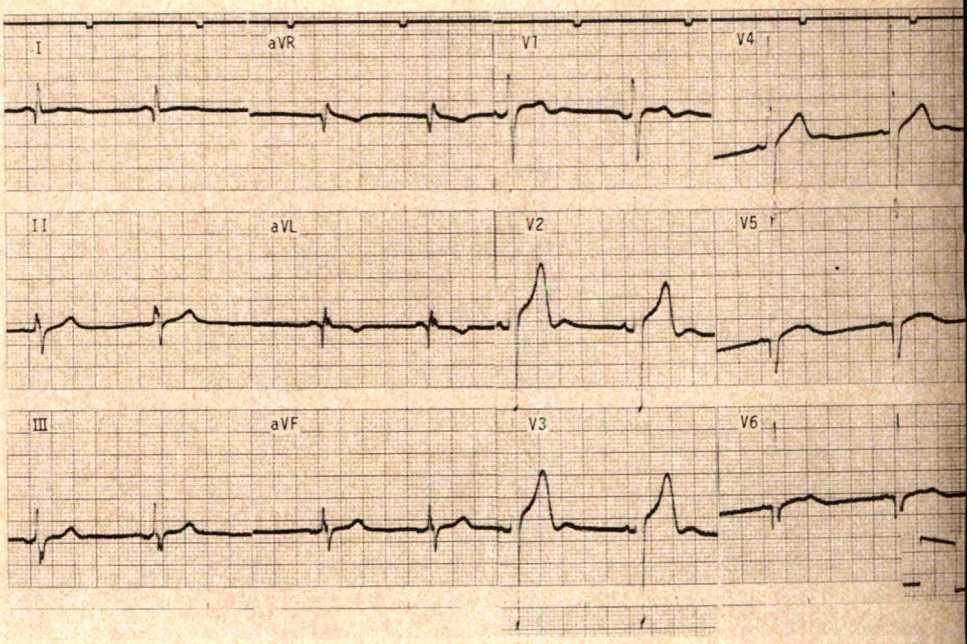


FIGURE 5. Case 2. Electrocardiogram showing A-V junctional rhythm with abnormal Q waves and QRS notching.

TABLE I

Reported Cases of the Kugelberg-Welander Syndrome with Symptomatic Cardiomyopathy

Case no.	Reference	Age (yr) & Sex	Cardiac Symptoms	ECG	HBE	Biopsy
1	Sterz et al.[21]	35M	Exertional dyspnea, Adams-Stokes syndrome	A Fib, A-V block with idioventricular rhythm, implanted cardiac pacemaker	—	—
2	Sterz et al.[21]	29M	Cardiomegaly	A Fib	—	—
3	Matsumoto et al.[232]	23M	Cardiomegaly, ascites, hepatomegaly, edema	Atrial standstill with A-V nodal rhythm, low voltage of QRS	—	—
4	Sugimura et al.[23]	23F	Exertional palpitation	SVPB, 1° A-V block, PAT, A-V nodal rhythm	A-H block	Fibrosis of RA; normal RV
5	Sugimura et al.[23]	31M	Dyspnea, cardiomegaly	A Fib, APB, left axis deviation, coronary type T wave, slurred R	—	—
6	Present report	24M	Precordial distress, cardiomegaly	AF, complete A-V block	A-H block	—
7	Present report	26M	Exertional palpitation, cardiomegaly	Deep Q in leads I, aVL, V_5 to V_6, notched QRS, RS in V_1	Normal	Fibrosis of RV

AF = atrial flutter; A Fib = atrial fibrillation; APB = atrial premature beats; A-V = atrioventricular; ECG = electrocardiogram; HBE = His bundle electrogram; LVH = left ventricular hypertrophy; PAT = paroxysmal atrial tachycardia; RA = right atrium; RV = right ventricle; SVPB = supraventricular premature beats.

e presence of atrial disease because right atrial fibrosis as demonstrated in a patient who had this disease and rial arrhythmias (Sugimura's Case 1)[23] and because rial standstill was observed in another patient (Matimoto's case).[22] Conduction disturbances (particularly dvanced A-V block, found in two patients (Sterz's ase[21] and Case 2 in our study) suggest the presence of ganic lesions in the A-V conducting system in this ndrome. Cardiomegaly, frank heart failure and the athologic changes in the right ventricle demonstrated our study indicate that the ventricular myocardium so may be involved. We also observed some degenered myocytes showing preferential loss of myosin laments[24] in the myocardium from a patient with ugelberg-Welander syndrome (unpublished data). herefore, the atrium, the A-V conducting system and ie ventricular muscle may be involved together, alough atrial arrhythmias are the most frequent clinical ndings.

Echocardiogram: Echocardiographic findings in the ugelberg-Welander syndrome have not previously een reported. Both the right ventricular and left atrial mensions were increased in Case 1, suggesting right ntricular and left atrial enlargement. An undulatory ttern of both mitral valve leaflets, both tricuspid valve aflets and interventricular septum occurred during rial flutter with A-V block. The pattern is caused by atrial flutter.[25] To our knowledge, this is the first report of such a pattern in the tricuspid valve.

Neurogenic and myopathic changes: From studies of muscle biopsy specimens, electromyograms and blood chemistry data, both neurogenic and myopathic changes have been found in the skeletal muscle in this syndrome.[26–28] However, it is controversial whether the primary site of the lesion is the anterior horn cells or both the anterior horn cells and the skeletal muscle itself.[26–28] It remains to be determined whether the lesion of the anterior horn cells, with or without dystrophic changes in skeletal muscle, is related to that of atrial and ventricular working myocardium and the A-V conduction system of patients with the Kugelberg-Welander syndrome. It seems necessary from the practical and etiologic standpoints that more attention be drawn to the cardiac changes in the heredofamilial degenerative diseases, including those in which the association with cardiomyopathy is thought to be uncommon.

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Coronary Arteriography for Everyone?

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A 52 year old lawyer once had chest pain on the golf course and comes to your office for a "heart check up." He is fully active and asymptomatic now. The history you take suggests a classic episode of angina pectoris. The physical examination reveals no abnormalities, and the electrocardiogram is normal. You make no specific recommendation and ask him to return to see you if the symptoms recur. The next week he dies of an acute myocardial infarction.

This tragic but not uncommon history raises a number of questions:

1. Should coronary arteriography be performed in everybody to rule out coronary artery disease? Of course not.
2. Should coronary arteriography be performed in all patients with a diagnosis of coronary artery disease?
3. Should coronary arteriography be limited to patients considered surgical candidates?

Let us analyze the data currently available in an attempt to answer the last two questions.

Prognostic Implications of Coronary Artery Disease

Numerous publications have shed light on the natural history of coronary artery disease, but have failed to precisely define it. Richards et al.[1] followed up 456 patients with angina pectoris for 25 years. At the end of the follow-up period, 445 were dead. Angina pectoris imposed an excess annual mortality over the expected survival of the group of 7 percent for men and 5.3 percent for women. The Framingham study[2] showed that within 8 years from the onset of angina pectoris 40 percent of all men and older women died. Forty-four percent of these deaths were sudden. Early studies documented [2,3] that 25 percent of all men with angina pectoris had an acute myocardial infarction within 5 years and that half of the men over 45 years old with angina pectoris had an acute myocardial infarction within 8 years, an annual incidence rate of 6.3 percent. These earlier series did not have angiographic confirmation of coronary artery disease. Patients with angina pectoris and a history of acute myocardial infarction tend to have a worse prognosis than those with angina and no previous myocardial infarction, particularly if they have triple vessel disease.[4,5]

The following clinical findings have been studied in patients with documented coronary artery disease for their predictive prognostic value.[6,7] Age, smoking and obesity have been found to be of little prognostic importance. Cholesterol level has been shown to be unrelated to 5 year mortality. Diabetes and hypertension have some prognostic significance, mostly related to a high proportion of multiple vessel involvement. The duration of symptoms has limited influence on prognosis since the high mortality rates in those with longer duration of symptoms are explained by a greater incidence of multiple vessel involvement. The character of symptoms, that is, atypical chest pain or stable angina (class I, II, III or IV), is poorly related to prognosis and to the severity of coronary arterial involvement.[6–8]

The electrocardiogram has a limited prognostic or predictive value. The prognosis is better when the patient has a normal electrocardiogram and worse when a pattern of myocardial infarction or conductive abnormalities are evident.[7] In patients with a normal electrocardiogram the prognosis will depend on the number of coronary arteries involved.

Exercise testing is more sensitive than a normal resting electrocardiogram for the diagnosis of possible

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coronary artery disease and has a better prognostic value. The percentage of positive results increases with the severity of coronary artery disease[10] and very positive results are associated with multiple vessel involvement.[11] The problem of false positive and false negative results has not yet been resolved and requires clarification.

The coronary arteriogram is important for the evaluation of prognosis. It has been demonstrated that the prognosis is directly related to the number of vessels involved[5–8] and to left ventricular function.[9] The prognosis becomes worse as left ventricular function deteriorates[9] and the number of vessels involved increases.

These findings indicate that the 5 year mortality of patients who are asymptomatic depends mainly on the severity of coronary arterial involvement and left ventricular function; they also indicate that the prognosis in patients with one, two or three vessel disease is not significantly altered by the clinical findings. Therefore, the coronary arteriogram and analysis of the left ventriculogram provide the most accurate means of evaluating the prognosis in coronary artery disease.

Coronary Arteriography: Risk and Benefits

Coronary arteriography is today a procedure that can be performed with a high diagnostic yield and low morbidity and mortality rates. A nationwide study of 176 hospitals that performed 89,079 coronary angiograms in 1973 and 1974 showed a 0.10 to 0.30 percent mortality rate for studies performed with the brachial technique and a 0.15 to 0.16 percent mortality rate for those performed with the femoral percutaneous technique.[12] In an earlier report from the same investigation,[13] mortality was related to the experience of the angiographer (1.4 percent mortality rate in hospitals performing less than 50 cases a year versus 0.09 percent mortality rate in those performing more than 800 cases a year), and the rate of complications was directly related to the duration of procedure.

The major contraindications for coronary arteriography are severe associated diseases, gross obesity, inadequate equipment and, most importantly, an inexperienced angiographer.[14]

Among patients undergoing coronary arteriography with the diagnosis of chest pain, 17.6 to 31 percent are found to have no obstructive coronary artery disease and can be advised to lead an active life.[15–18] At the other extreme, 2.7 to 6 percent of all patients undergoing coronary arteriography are shown to have significant obstruction of the left main coronary artery.[11,19] Between these two extremes, differing but significant proportions of patients are found to have single, double and triple vessel involvement.

Several centers have accumulated a large experience with coronary angiography performed on an outpatient basis. No additional risk for the patient is reported. Therefore, it is entirely possible that this modality might allow future study of a large population of persons with proved or suspected coronary artery disease at a minimal patient and hospital cost.

Surgical Treatment of Coronary Artery Disease

Coronary bypass surgery can be performed with a low surgical mortality rate of 0.7 to 5 percent.[20–23] Surgical results in relation to symptomatic improvement have been excellent[24] and are correlated with the completeness of revascularization. In patients with complete revascularization, 86.6 percent became completely asymptomatic and 11.7 percent were in functional class II (criteria of the New York Heart Association); only 1.6 percent remained in functional class III and no patient has class IV symptoms.[25] The correlation between symptomatic relief, completeness of revascularization and graft patency is supported by results of exercise testing.[26]

Recent reports from various centers now provide persuasive evidence that myocardial revascularization performed by skilled teams improves the survival rate in patients with double and triple vessel disease.[20,23,27–30]

The Diagnostic Approach to Coronary Artery Disease

With all these data currently available to the physician treating patients with coronary artery disease, it appears imperative that he consider coronary angiography: (1) to ascertain that the diagnosis is correct, and (2) to determine the stage of the disease in each individual patient as the basis for making logical decisions regarding proper therapy. It is vital that there be appreciation of the relative unreliability of clinical criteria that heretofore have been used as indexes of severity and prognosis (age, functional class, duration of symptoms, resting normal electrocardiogram, and so forth). Furthermore, current concepts of clinical practice require that the patient as well as the cardiologist be aware of the severity (or lack of severity) of the disease and its implications.

The appropriate diagnostic evaluation of the 52 year old lawyer who consulted a cardiologist for objective and quantitative information regarding "his heart," should have included an exercise tolerance test and coronary arteriography. If it had been found that he had severe multiple vessel involvement, revascularization surgery would have been the appropriate recommendation, thereby significantly improving his chances for survival. If single vessel involvement had been discovered, particularly of the right or the circumflex coronary artery, intensive medical therapy would have been recommended. In this specific case, the chances for survival appear to be similar to those of surgical therapy.

The history of this patient constitutes a representative example of the need for coronary arteriography as part of the evaluation of the patient with coronary artery disease, and of some of the consequences resulting from the management of these patients without the information provided by coronary arteriography. It is possible that in the future noninvasive techniques will provide the clinician with enough information regarding the extent and severity of coronary artery disease to permit a more limited selection of patients for coronary angiography.

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Coronary Arteriography: Selection of Patients

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The editorial by Pichard[1] is an example of the change in thinking about coronary artery disease that has come about in the last 10 years. Many people rejected the idea of coronary arteriography during its infancy. Perhaps this skepticism was justified because surgical treatment of coronary disease was then limited to techniques of questionable benefit. The clinician had few alternatives to clinical diagnosis and treatment using drugs that did not change the natural history of the disease. It was popular to reserve consideration of surgical treatment for patients with uncontrollable pain. Fortunately, aggressive surgical groups improved their approach to the problem and developed direct revascularization techniques that are still in need of long-term evaluation but have already increased the survival time of selected patients.

Obviously, a disease so unpredictable in its manifestations and progression, and so lethal, justifies a radical approach in an effort to improve the miserable results recorded in the past. I suspect that the trend will be toward more aggressive coronary arteriographic study and that Pichard has indicated the direction of future diagnosis and treatment.

I have, at present, a somewhat more reserved position. I believe that patients who have a normal exercise electrocardiogram at near maximal heart rate do not have active myocardial ischemia and are at low risk for coronary death. This is not to say that they do not have coronary artery disease, either arteriosclerotic or spastic in nature. Since there is some risk, although it is small, to the patient undergoing coronary arteriography, we can certainly select for arteriographic study a subgroup of patients at high risk, such as those with positive exercise electrocardiographic tests. There are clear exceptions to this dogmatic grouping: Knowledge of the anatomic distribution of coronary artery disease will not change the treatment plan of some patients because they have other serious disease; by contrast in some patients with previous myocardial infarction and a negative exercise test the psychological benefit alone is enough to justify arteriographic demonstration of the coronary arteries.

These views may be considered reactionary in the next few years, but at present I have a philosophic reservation to recommending coronary arteriographic study to every patient with chest pain. What of the patients without pain? If one extends the fundamental thesis of prolonging life, then one has to be concerned about those patients with coronary disease who never have pain (neuropathy in some diabetic patients?) and patients who have shortness of breath on exertion (ischemic decrease in left ventricular compliance?) but who have no pain. Should we conclude that all men over age 40 years and all women 5 years after the menopause should have prophylactic study?

The exercise electrocardiogram is not the perfect answer, but it is the only tool we now have for making some reasonably noninvasive selection of patients at risk. The rapid expansion of radioisotope techniques and their many potential applications to the study of the metabolism and perfusion of the heart during exercise, and particularly in the identification of ischemia, offer hope that in the near future we will have other noninvasive aids in selecting the patient at risk who needs arteriographic study.

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Coronary Arteriography 1976—For Whom?

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The introduction of selective coronary angiography by Sones and Shirey[1] has brought about major advances in the evaluation and treatment of coronary artery disease. Selective coronary arteriography can precisely define the extent and distribution of coronary disease in man during life. As a result of Sones' contributions, interest in direct coronary revascularization was renewed so that now surgical management of coronary artery disease has become routine in many large medical centers. Despite 8 years of extensive clinical experience, the indications for operative intervention remain unclear in many clinical situations. A major difficulty is determining which subjects are in need of arteriographic study, for in order to make rational decisions both the natural history of coronary artery disease and the long-term effects of surgical treatment must be known.

Current Patterns of Practice

In our institution, selective coronary angiography is performed for a variety of indications. Angiographic studies are performed to (1) evaluate patients with angina pectoris being considered for surgery; (2) assess the results of saphenous vein bypass graft surgery; and (3) evaluate patients with chest pain of unknown origin.

Surgical management of cornary artery disease is commonly accepted practice in patients with (1)severe angina pectoris unresponsive to optimal medical management who have adequate distal runoff and reasonably good left ventricular function; and (2) severe left main coronary disease with 75 percent or greater narrowing of luminal diameter. However, indications for surgical management of patients with several other clinical conditions is less clear. This group includes (1) patients with preinfarction angina; (2) patients with nondisabling stable angina; (3) patients who, after their first or second myocardial infarction, are asymptomatic; and (4) asymptomatic patients who have had one or two anginal episodes in the past.

Although others, such as Pichard,[2] might take a more aggressive stance and recommend coronary angiography for all patients suspected of having coronary artery disease regardless of their symptoms, we now take exception to this approach because it presupposes that there have been definitive studies clearly demonstrating that surgical therapy prevents myocardial infarction and promotes longevity. This is not yet the case.

It is generally agreed by most cardiologists that coronary bypass surgery relieves or abolishes anginal symptoms in 80 to 90 percent of patients. Results of longer follow-up studies from many centers suggest that 75 percent of survivors remain improved symptomatically even 4 years after surgery.[3] Objective as well as subjective improvement has been noted as evidenced by increased exercise tolerance and improved hemodynamic status, both of which correlate well with graft patency.[4,5] Thus, there is little question concerning the immediate value of coronary surgery. What effect coronary surgery will have on the survival of the patient with coronary artery disease remains to be seen.

Several surgical groups have now reported prolonged survival for surgically treated patients by comparison with medically treated patients.[6,7] However, most surgical studies are retrospective, fail to define subgroups and lack randomization. Nevertheless, some cumulative surgical experience suggests that survival is in fact prolonged and that symptoms are significantly relieved in selected subsets of patients. One such set is composed of patients with severe occlusion of the left main coronary artery. The outlook for these patients is grim when they are treated medically[8,9]; surgical intervention has improved both survival rate and functional capacity.[9,10]

Another group of patients that might benefit from surgery are those with unstable or preinfarction angina. The variability in definitions and the lack of general agreement as to what constitutes preinfarction angina have made objective assessment of this group extremely difficult. Thus, reported mortality rates for such patients range from 3 to 40 percent.[11] The marked disparity in these figures is obviously due to differences in the rigor with which the preinfarction state is defined. Adherence to a rigid definition (severe chest pain at complete bed rest, transient reversible S-T segment depression of 2 mm or more occurring with pain and no electrocardiographic or enzyme evidence for acute myocardial infarction) permitted identification of a subset of patients truly at high risk for myocardial infarction.[12] Emergency surgical therapy performed immediately after angiographic evaluation decreased the rate of infarction and improved survival rate. Conti et al.,[11] reporting on a similar group of patients, found no significant difference in morbidity and mortality be-

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tween the surgically and medically treated groups. A more detailed study of this unstable group of patients is clearly needed.

Goals and Future Directions

The overwhelming consensus is that most patients with severe angina unresponsive to optimal medical management improve symptomatically after coronary bypass surgery. That the operation improves the quality of life in these patients is incontrovertible and, since it is clear that surgery does not shorten survival time, operative intervention will be the mainstay of therapy in this group and justifiably so.

But what about the clinical situations previously alluded to? Should all patients with known or suspected coronary artery disease undergo coronary angiography? Does a single episode of angina pectoris dictate the need for coronary angiography? Serial angiographic studies performed in all patients with suspected coronary artery disease would unquestionably provide objective data on the natural history and progression of coronary atherosclerosis, but such a procedure is certainly not warranted. At least not until or unless prospective studies demonstrate unequivocally that coronary bypass surgery prevents myocardial infarction and increases long-term survival.

Until then, we as clinicians should strive to identify patients at high risk of having an acute myocardial infarction or death. Patients with severe angina at rest or on minimal exertion associated with inordinate prolonged shortness of breath may have left main coronary disease or severe multivessel disease[8,13] and should be studied. Similarly, patients satisfying the criteria cited for preinfarction angina should undergo coronary angiographic evaluation. Other patients at high risk can be identified with noninvasive techniques.

A readily available and widely used tool is the postexercise electrocardiogram, which provides information not available from coronary angiography alone. The various exercise tests, which are easily performed and relatively free of risk, attempt to test the physiologic adequacy of the myocardial blood supply. They are by no means capable of ferreting out all patients with coronary artery disease from the normal population but, when performed carefully and interpreted properly (so important!), they do identify patients who are at high risk of having a major coronary event. Several studies[14–16] have shown a good correlation between the number of angiographically demonstrable diseased coronary vessels and the frequency and degree of abnormality in the postexercise electrocardiogram. Thus, 95 percent of patients with S-T segment depression of 2 mm or more had two or three had vessel coronary artery disease, and 72 percent had three vessel disease.[14]

Robb and Seltzer[17] recently reviewed the results of the Master double two-step test administered to 3,325 male applicants for life insurance who were then followed up for an average of 9 years. They found that the degree of ischemic S-T segment depression was related to the severity of coronary artery disease and ultimately to prognosis. Thus, the mortality rate in their grade III cases (2 mm or more depression) was 6 times greater than in grade I cases (less than 1 mm depression). The observation that a severe degree of S-T depression indicates the presence of severe triple vessel disease[14,16] and a poor prognosis[17] lends a quantitative capability to the exercise electrocardiogram and identifies the high risk patient.

Another promising area of investigation utilizes radionucleotides in assessing the adequacy of myocardial blood flow. Along with potassium-43, cesium-129 and rubidium-81, thallium-201 is an intracellular monovalent cation that concentrates in normal myocardium in direct proportion to the coronary blood flow. Although still in the early stages of evaluation, thallium-201 appears to have the best biologic and physical characteristics of this group of isotopes. With the new high resolution gamma scintillation cameras now available, measurement of myocardial ischemia by thallium-201 imaging has become feasible. With this technique areas of ischemia or infarction appear as zones of decreased tracer uptake, that is, perfusion defects.

Since physiologic studies have demonstrated that normal resting flow can occur in coronary arteries with 50 to 70 percent narrowing of the luminal diameter, it should not be surprising that myocardial perfusion images obtained at rest in this setting might well be normal.[18] However, scans performed during the stress of exercise will readily identify these patients. Areas of myocardium supplied by a critically narrowed artery cannot experience a significant increase in the coronary blood flow during exercise and will therefore show up as a perfusion defect. The larger the defect the greater the area of ischemia. Zaret et al.,[19] using potassium-43, have suggested that a perfusion defect noted both at rest and during exercise is indicative of myocardial scarring, whereas an abnormal scan noted only during exercise is due to transient myocardial ischemia. A normal myocardial perfusion scan during stress rules out a hemodynamically significant coronary lesion with a high degree of certainty.

In our present state of knowledge, angiographic evaluation of presumed patients at low risk is not justified. However, an urgent need exists for reliable data regarding the effects of coronary artery bypass surgery in patients with ischemic heart disease at high risk of having a major coronary event. Patients in this category should be evaluated hemodynamically and angiographically, placed in several sharply defined clinical subsets and entered into a randomized prospective study comparing short- and long-term results of coronary bypass surgery with those of medical management. For such data to be meaningful the severity of the disease must be precisely defined anatomically and physiologically. The subsequent clinical course and the surgical and medical management must be meticulously defined. The data derived from patients managed operatively must be compared with the clinical course of similar patients characterized in the same fashion but treated medically. Information derived from this type of study will enable us to make individual recommendations for therapy on a more rational basis.

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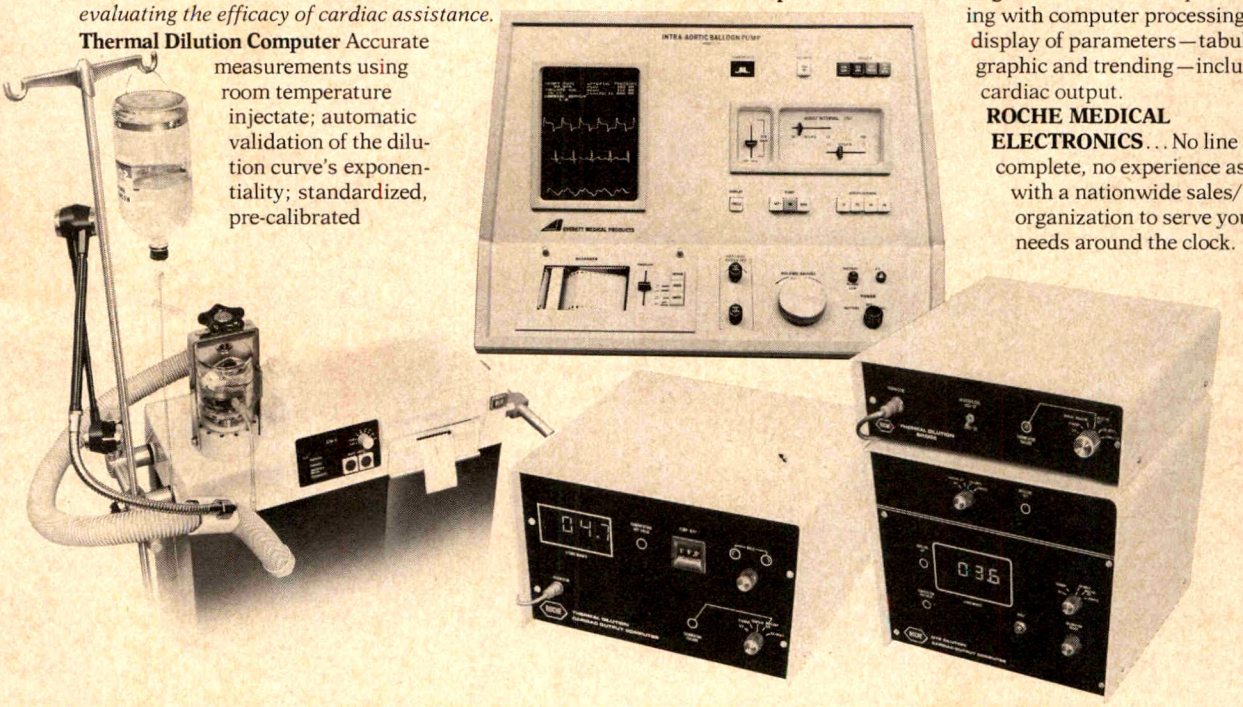
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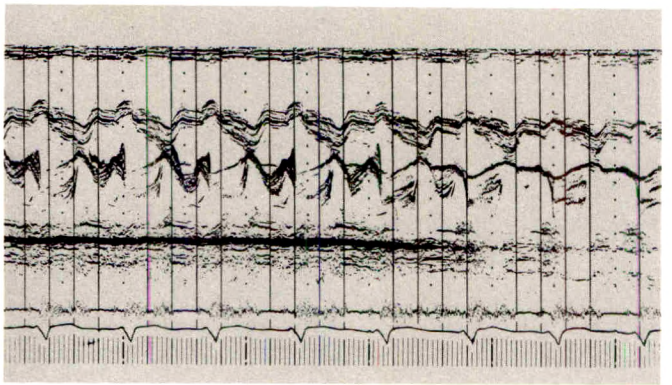
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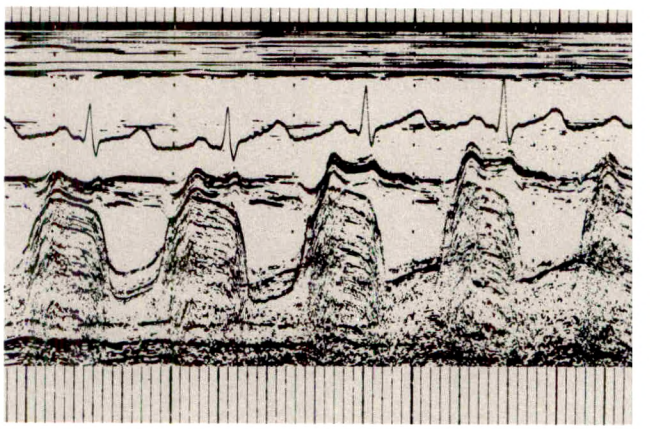
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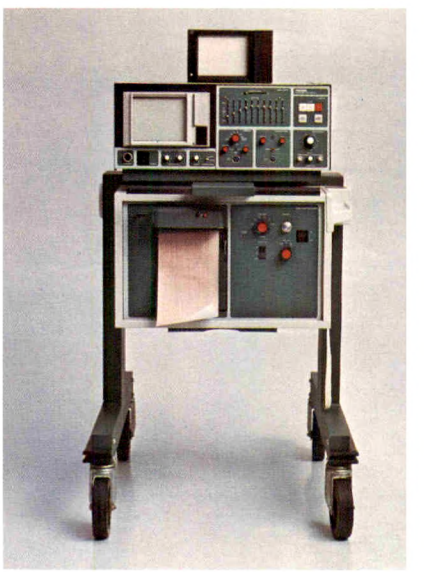
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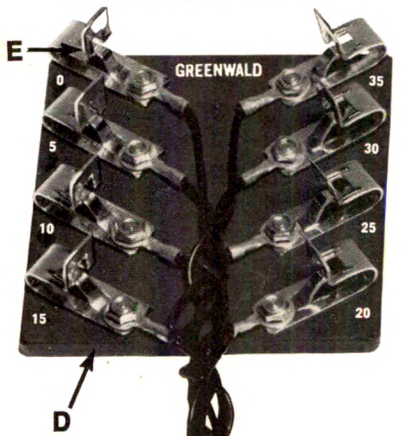
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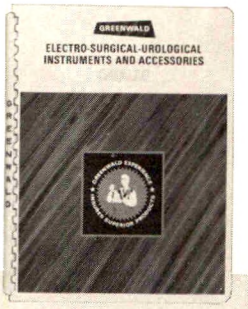
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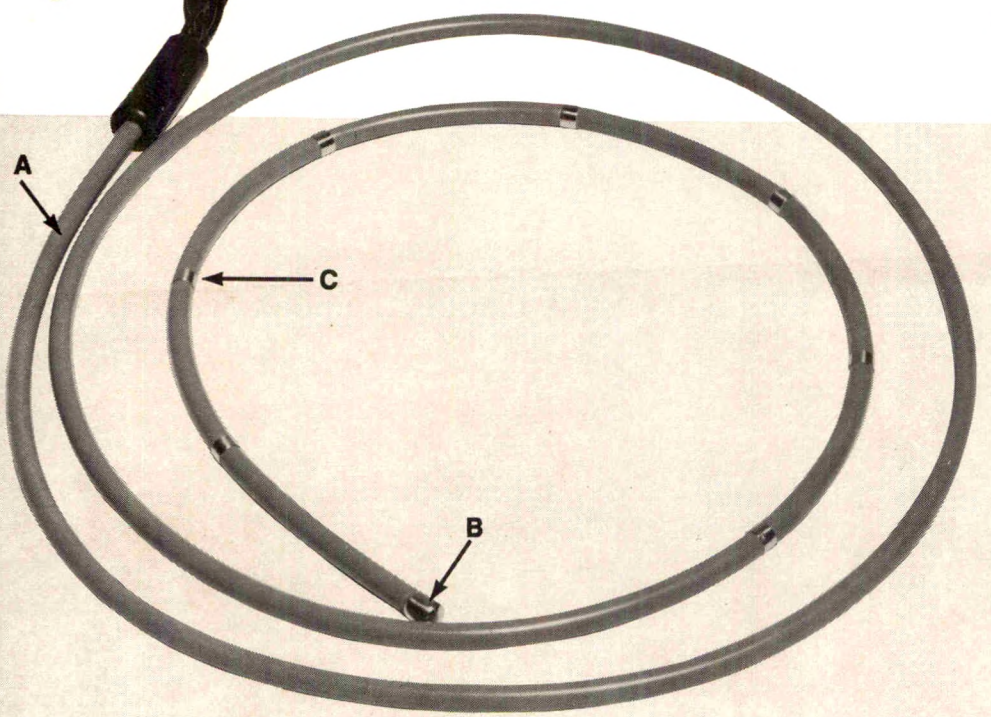
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PHASIC LEFT VENTRICULAR BLOOD VELOCITY ALTERNANS IN MAN

The article by Desser and Benchimol[1] may be "the first comprehensive description of left ventricular blood velocity alternans in man," but the implication that man is different from other species in terms of basic myocardial mechanisms is a dangerous one. It permits the authors to ignore a large body of animal experiments performed with superior technology, measurement of more independent variables and more control over circumstances. In addition, it becomes a rationalization for subjecting patients to procedures with real risk for data that are not new.

The authors measured velocity with a Doppler catheter flowmeter. (They emphasized radiotelemetry in the abstract, but there is no advantage to telemetry for transmission of information in a catheterization laboratory, where one more wire would make very little difference.) They imply that their beat to beat blood velocity measurements are superior to beat to beat pressure measurements previously reported from many clinical centers, but it is physically unreasonable to expect any qualitative differences: Resistance to flow requires 10 to 15 seconds for a substantial change. In actual measurements under controlled conditions, the single best predictor of beat to beat systolic pressure was the peak flow velocity.[2] This relation is based on physics rather than species and cannot easily be ignored. One could use a noninvasive transcutaneous Doppler flow measurement of the brachial artery, or any other artery, if something beyond pressure was desired. Peak velocity is only that, and does not constitute stroke volume measurements; these would require fixation of the catheter and certain knowledge of the cross-sectional area of the aorta at the site of measurement.

We studied pulsus alternans in dogs with measurement of left and right ventricular stroke volumes, peak velocity, aortic and left ventricular end-diastolic pressures and continuous measurements of the left ventricular diameter.[3] Our data made a strong case against the possibility that alternans was caused by "beat to beat variations in end-diastolic fiber length." We found a wide variation between the end-diastolic fiber length and left ventricular stroke volume. In fact, the correlation coefficients were frequently negative. In addition, by mathematical modeling, we showed that heterometric autoregulation should dampen out pulsus alternans very quickly rather than cause sustained alternans. In this regard, the "classic high-low phenomenon," which the authors fail to attribute to anyone, was first shown in our study. This phenomenon is important, since alternation was previously attributed to a normal beat alternating with a weak beat, whereas our data showed alternation between a potentiated beat and a weak beat. This observation led to the conclusion that the cause of most instances of alternation was alternating inotropic state.

Physicians owe it to their patients to learn as much as possible about illnesses, but at the lowest risk possible for the patient. Animal studies present that opportunity, particularly when the mechanisms involved are quite basic. I suggest that journals have an ethical obligation to discourage studies with risk to patients that do not add substantial information to the body of knowledge about a pathologic process such as alternation.

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2. **Guntheroth WG, Morgan BC, Mullins GL:** Effect of respiration on venous return and stroke volume in cardiac tamponade. Circ Res 20:381–390, 1967
3. **Guntheroth WG, Morgan BC, McGough GA, et al:** Alternate deletion and potentiation as the cause of pulsus alternans. Am Heart J 78:669–681, 1969

REPLY

1. The implication that other species are identical to man in terms of basic myocardial mechanisms is a dangerous one. Fortunately, investigators interested in human cardiac alternation have available a substantial number of references based on data obtained with "superior technology" from man. If "control over circumstances" implies alteration of independent or dependent variables during experimentation, then the results become even further removed from the setting of the natural phenomenon.

2. It is possible that right ventricular pacing and intravascular blood flow measurement as performed in Guntheroth's laboratory represent a major patient risk. If that is the case, then we definitely agree that he should restrict his activities to experimental animals. During the past few years we have performed rapid right ventricular pacing and simultaneous intravascular blood velocity measurements on more than 5,000 occasions in 1,000 patients. Such study has not been associated with a single untoward incident. This record compares favorably with most statistics cited for routine intravascular study in man.

3. If Guntheroth prefers having unnecessary extra wires in his catheterization laboratory, then that is his prerogative.

4. We did not imply that beat to beat blood velocity measurements were superior to pressure measurements. Guntheroth's statements regarding pressure and flow are unsound. If pressure is related to the product of flow and resistance then: (a) It is physically reasonable to expect qualitative differences between blood velocity and pressure in nonrigid chambers. Such phenomena are well documented. (b) Resistance to flow does not require 10 to 15 seconds for a substantial change. (c) Peak flow velocity may be directly related to peak intravascular pressure during basal conditions in dogs but these two measurements are *not* uncommonly discrepant during cardiac arrhythmias in man.

5. The blood velocity levels described in our paper were recorded within the left ventricle. If the study was concerned with brachial arterial blood velocity then a transcutaneous Doppler velocimeter might have proved useful. In fact, we have demonstrated the advantage of that method.

6. Comments relating to aortic cross-sectional area are not relevant since the blood velocity measurements were made within the left ventricle. Interestingly, weaker ventricular contractions producing decreased stroke volumes, generally produce lower aortic peak blood velocities. We believe that these relations do not occur by chance alone.

7. The purpose of our paper was not to resolve controversy concerning the underlying cause of mechanical alternation. On page 313 we considered the possibility of disparate end-diastolic fiber lengths or differences in inotropic state as mechanisms responsible for pulsus alternans. Other investigators concentrating on this aspect of alternation could probably present equally forceful arguments supporting their views on the subject. On the other hand, Guntheroth's results in no way conclusively prove that alternate deletion of contractile elements is the sole cause of pulsus alternans. Oddly, the phasic flow recordings in figures from his paper do not contain calibration standards. The method utilized for stroke volume estimation in dogs with large diameter thick-walled Silastic® tubes passed into the left ventricle through an apical incision is open to question.

8. In human subjects, alternation is not confined to potentiated and weak beats. Normal beats may alternate with weak beats, and all combinations have been observed.

9. Classic "high-low" alternation was demonstrated before publication of the paper of Guntheroth et al.

10. We are not aware of any other study in experimental animals or man that has demonstrated rate-related shifts of concordant and discordant blood velocity alternans, variant 2:1 blood velocity alternation or diastolic blood velocity alternans at the mitral valve during cardiac pacing. If Guntheroth has subjected similar data to editorial review and it has been published then our observations are "not new." To date, we cannot find such data.

11. Physicians owe it to their patients to learn as much as possible about various cardiac disorders at low risk, as in our investigations of blood velocity during pulsus alternans. New phenomena demonstrated in animal studies should not be considered identical with those occurring in human subjects. Journals have an ethical obligation to discourage unfounded and uninformed letters that do not add to our knowledge of mechanical alternation.

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ATRIAL PACING VS. EXERCISE TESTING

Rios and Hurwitz[1] recently reported atrial pacing to be less sensitive than exercise stress testing in the diagnosis of coronary artery disease. They did state that two major drawbacks of atrial pacing were (1) difficulty in interpretating S-T segments during rapid pacing, and (2) frequent occurrence of atrioventricular (A-V) conduction defects at higher pacing rates.

We have been impressed with the efficacy of two modifications in the technique of atrial pacing: (1) If the patient experiences anginal pain during pacing but the S-T segment changes are difficult to interpret, pacing is stopped abruptly. The S-T segment changes in the next few sinus beats are usually characteristic and undistorted by pacemaker artefacts (Fig. 1). (2) The intravenous administration of atropine (1.0 mg) abolishes the A-V conduction defects in 77 percent of cases.[2] Thus, higher pacing rates, up to 220 to 240 beats/min, can be achieved with an increased yield of positive test results.

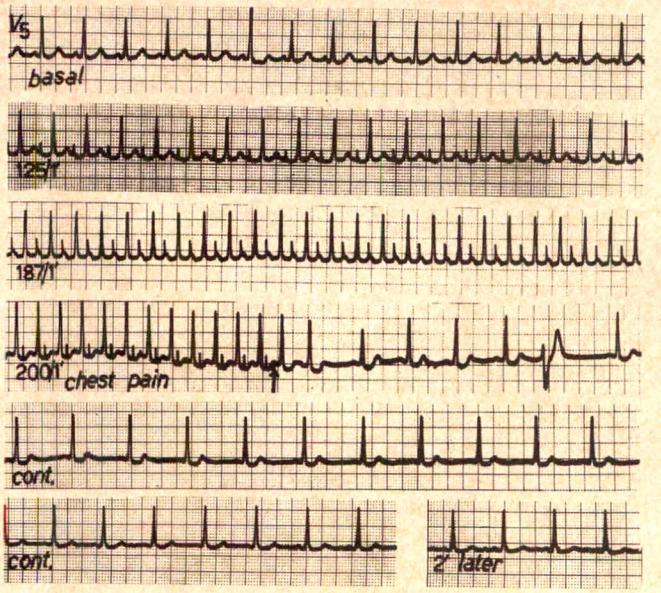


FIGURE 1. A 54 year old man with typical history of angina pectoris. Chest pain occurs only at pacing rates of 200/min, when S-T segment interpretation is impossible. However, after abrupt cessation of pacing (**arrow**) typical ischemic S-T depression is seen, regressing after about 18 sinus beats.

With the use of these refinements we have observed a sensitivity of more than 90 percent in the diagnosis of angiographically proved coronary artery disease. We thus believe that atrial pacing is superior to exercise tests in sensitivity.

Dennis V. Cokkinos, MD
Evangelismos Hospital
Athens, Greece

Reference

1. **Rios JC, Hurwitz LE:** Electrocardiographic responses to atrial pacing and multistage treadmill exercise testing. Am J Cardiol 34:661–666, 1974
2. **Cokkinos DV, Katsaros S, Grivas P, et al:** Use of atropine for higher right atrial pacing rates. "Maximal" pacing for diagnosis of coronary artery disease. Br Heart J 35:720–728, 1973

REPLY

We concur with Cokkinos' observations that the intravenous administration of atropine sulfate enhances A-V conduction properties and therefore permits a faster ventricular rate by maintaining 1:1 conduction as a result of a shorter A-V node refractory period.

The discrepancy in results published in our study and those reported by Cokkinos clearly rests on the different heart rates analyzed. That atrial pacing at 220 to 240 beats/min was necessary to obtain positive results supports our contention that "the reduced ability of atrial pacing to cause an electrocardiographic ischemic response is probably due to differences in hemodynamic effects of the two testing methods" (atrial pacing vs. exercise) and that "the myocardial wall tension and stress of comparable heart rates may be lower during pacing than during exercise." Furthermore, the rates utilized by Cokkinos are higher than the physiologic heart rate obtained during maximal exercise in subjects aged 34 to 68 years. The physiologic consequences of these extremely rapid rates may

result in decreased diastolic filling period, end-diastolic volume, stroke volume and coronary flow.

Other methodologic differences between the two studies make comparison of results difficult to evaluate. Some difficulties are the use of the Master two-step test versus multistage treadmill exercise, the differences in population sample and the difficulty in comparing the similarities in coronary occlusive disease. Cokkinos has concluded that "atrial pacing is superior to exercise testing in sensitivity." The work of Barnard et al.[1] is relevant here. They demonstrated an abnormal electrocardiographic response in 6 of 10 normal subjects after performing sudden strenuous exercise. When the same exercise was performed after a warm-up period only 2 of the 10 subjects had an abnormal electrocardiogram. They attributed the number of false positive results to a transient unfavorable alteration in subendocardial oxygen supply/demand relation.

Until data on the sensitivity of atrial pacing at these rapid rates are compared with data on its specificity the absolute merit of the modified atrial pacing test cannot be assured and we therefore cannot agree with Cokkinos' conclusions.

Jorge C. Rios, MD
George Washington University Medical Center
Washington, D. C.
Larry Hurwitz, MD
University of Pittsburgh, School of Medicine
Pittsburgh, Pennsylvania

Reference

1. **Barnard RJ, MacAlpin R, Kattus AA, et al:** Ischemic response to sudden strenuous exercise in healthy men. Circulation 48:936–942, 1973

S-T ELEVATION AFTER INFARCTION

Mills et al.[1] appear to have made a substantial contribution to our knowledge of postinfarction S-T evolution and its significance. I think it would be helpful if they submitted raw data documenting so many unresolved S-T elevations for up to 6 months after anterior infarction—specifically, actual electrocardiograms for several cases showing the S-T elevation in leads V_2 to V_4. In normal electrocardiograms at least, there is usually no S-T "segment" in medial precordial leads, particularly leads V_1 and V_2, if these are predominantly of rS configuration. (Indeed, we often see where S-T "segments" begin, but their end is often a mystery.) In rS leads, the T wave tends to "dogleg" up from the J point and any "segment" isoelectric with the T-P interval could be considered depressed. Thus it is common for normal precordial rS leads to have nearly all of the initial limb of the T wave well above the baseline, and resolution of some infarcts might in some patients result in a return to this preexisting configuration. On the other hand, if all the authors' patients with nonresolution had J junction elevation followed by a horizontal S-T segment (that is, a real *segment*), their point is made. In the absence of deep S waves, as in left ventricular hypertrophy, excessive J point elevation alone might qualify. But the authors cite the midpoint of the segment, and a segment should have a beginning and an end. Their exclusion of lead V_1 was appropriate. If the S-T changes predominated in leads V_4 and V_3 (versus in an rS-configuration lead V_2), their results would be even better substantiated. A precordial complex from four or five of their patients would clarify this completely.

I have no doubt that the outstanding group who have done this work will be able to demonstrate their criteria. The source of my confusion is in the larger context of what is an S-T "segment," at least in lead V_1 or V_4 in left ventricular hypertrophy (did some of their patients have left ventricular hypertrophy?) and in normal subjects with deep S waves, in whom the J point may appear elevated.

David H. Spodick, MD, FACC
Tufts University School of Medicine
Boston, Massachusetts

Reference

1. **Mills RM Jr, Young E, Gorlin R, et al:** Natural history of S-T segment elevation after acute myocardial infarction. Am J Cardiol 35:609–615, 1975

REPLY

Spodick's letter raises questions about which we debated for some time. To rephrase his questions into a more answerable syntax, they are: (1) How does one handle the problem of assessing degree of S-T segment elevation when the precise bounds of the segment are ill defined, and (2) How does one differentiate pathologic S-T elevation from the normal variant "early repolarization syndrome?"

To answer the first, one can be quite sure that there is a deflection that is definitely "QRS" and a deflection that is definitely "T wave" in most electrocardiograms. Rather than accepting Spodick's definition, we believe that the portion of tracing between the end of "QRS" and the apparent onset of "T" is of necessity "S-T segment." The configuration of this segment is highly variable and may be a fruitful area for electrocardiographic and vectorcardiographic research.

Spodick misquotes us on a critical term. He says, "the authors cite the mid*point*" (italics ours), whereas, in fact, we stated "mid-portion." We agree that it is very difficult, or impossible, to define a precise "mid-point" of an ill-defined S-T segment. However, for clinical purposes, it is possible and reasonable to define carefully an area of the tracing as lying about midway between "definitely QRS" and "definitely T" and deal with that area as the "mid-portion" of the S-T segment.

The second question reflects the viewpoint of an electrocardiographer often forced to interpret tracings without benefit of clinical data, as opposed to the clinician attempting to correlate electrocardiographic, physical and pathophysiologic data. Given only an isolated standard 12 lead electrocardiogram, showing S-T elevation in the mid chest leads without clinical data, a competent electrocardiographer may only be able to offer a differential diagnosis, such as "S-T elevation compatible with acute or resolving infarction, early repolarization," and so forth. However, when one has clinical documentation of myocardial infarction or angiographic demonstration of coronary artery disease and wall motion abnormalities, and in addition serial tracings demonstrate progressive QRS and S-T segment changes, then ascribing the observed electrocardiographic changes to the manifest coronary heart disease seems reasonable.

In summary, our observations were made within the context of clinically manifest coronary heart disease. Any datum can and should, be interpreted two ways: as an isolated finding having several possible interpretations and as a link in a consistent chain of knowledge about the process of coronary heart disease in a patient over a period of time. We appreciate the relevance of Spodick's comments to precision in the first area and acknowledge that the second is not a precise science.

Roger M. Mills, Jr., MD
Elliot Young, MD
Richard Gorlin, MD, FACC
Michael Lesch, MD, FACC
Peter Bent Brigham Hospital
Boston, Massachusetts

TRANSIENT Q WAVES: AN ANAMNESTIC RESPONSE OF AN OLD MYOCARDIAL INFARCTION

As Meller et al.[1] indicate, the transient Q waves in Prinzmetal's angina may reflect a severe ischemia of a localized area of myocardium, and electrical death is not synonymous with biologic death. We have recently proposed a new concept[2,3]: Transient Q waves may reveal an old myocardial infarction. Thus, patterns of an old myocardial infarction, that had long ago disappeared, may reappear in the electrocardiogram during an acute ischemic episode. In these cases, it is likely that the transient reappearance of Q waves is due to transitory ischemia of the superficial myocardial layer that surrounds the old infarcted area. During ischemia, this layer becomes electrically silent; the formerly infarcted area then appears "under" the electrodes, and a QS or QR pattern is recorded; when the superficial layer has recovered, the infarcted area is no more "in contact" with the electrodes, and R waves reappear.[4] Recent works support our view: Transient Q waves have been described during ischemia induced by atrial pacing[5] or isoproterenol provocation[6] in patients with a prior acute myocardial infarction. Knowledge that transient Q waves may appear as a temporary proof of an old and sometimes undiagnosed myocardial infarction is of importance since these waves are usually recorded during a new and severe ischemic episode with anginal pain and patients with them are usually referred with the wrong diagnosis: recent acute myocardial infarction.

Paul Chiche, MD, FACC
Rober Haiat, MD, FACC
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2. **Chiche P, Berkman M, Haiat R:** Ondes Q transitoires et à éclipse au cours de l'insuffisance coronarienne aigue. Arch Mal Coeur 64:657–659, 1971
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5. **De La Fuente DJ, Gambetta M, Goldbarg AN:** The significance of transient Q waves (abstr). Circulation 45,46:Suppl II:II-153, 1972
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REPLY

I fully agree that transient Q waves reflect electrical silence without biologic death in certain cases. This would explain, as we discussed it, the momentary appearance in our Case 2 of a pattern of anteroseptal myocardial infarction during the episodes of anterior wall ischemia. Their speculation that transient Q waves may reveal an old myocardial infarction can apply only to our Case 1, in which a transient pattern of inferior wall myocardial infarction appeared during every episode of anterior wall myocardial ischemia. But, in contrast to the view that old myocardial infarction is unmasked because of new ischemia to the opposite wall, it was proposed by Bassan et al.[1] that new Q waves seen in patients after coronary bypass might be due to improved coronary perfusion to ischemic areas opposite to the area of infarction. Such improvement thus relieved ischemia that had been canceling the loss of opposing forces of an old infarcted area. Both theories may be correct in different situations because the electrocardiogram is only the final expression of the balance of the electrical potentials, which are modified during myocardial ischemia and probably also after improvement of myocardial perfusion.

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Reference

1. **Bassan MM, Oatfield R, Hoffman I, et al:** New Q waves after aortocoronary bypass. N Engl J Med 290:349–353, 1974

"HOLOSYSTOLIC EJECTION MURMUR"

I was puzzled by the "grade 3/6 holosystolic ejection murmur that was heard at both the apex and the base" in Case 1 of Hirschfeld and Emilson[1] for aortic ejection murmurs do not extend up to the aortic component of the second heart sound to justify the term "holosystolic." [2] The patient might have a holosystolic murmur, presumably due to mitral regurgitation, or an aortic ejection murmur or, most likely, two separate murmurs (one holosystolic and one ejection) loud enough to be audible at both the apex and the base of the heart; but the use of the term "holosystolic ejection" to describe a murmur leads to confusion.

Incidentally, in the echocardiogram of the same patient (Fig. 2B) the space behind the aorta labeled the right atrium (RA) in reality is the left atrium.[3]

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Department of Medicine/Cardiology
Medical College of Georgia
Augusta, Georgia

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1. **Hirschfeld DS, Emilson BB:** Echocardiogram in calcified mitral annulus. Am J Cardiol 36:354, 1975
2. **Leatham A:** Auscultation of the heart. Lancet 2:757, 1958
3. **Feigenbaum H:** Echocardiography. Philadelphia, Lea & Febiger, 1972, p 146

REPLY

The term "holosystolic ejection" was meant to be descriptive rather than to imply a functional basis for the murmur. We have, in fact, utilized a simple noninvasive screening test for calcification of the mitral anulus: Patients are examined by two medical students; those patients who have a murmur described by one student as ejection in quality and by the other as holosystolic in timing are likely to have a calcified mitral ring. Ventricular septal defects also produce murmurs that may be described as both pansystolic and ejection in quality.[1]

The left atrium in the echocardiogram of our first patient was, as noted, incorrectly labeled.

David S. Hirschfeld, MD
Los Gatos, California

Reference

1. **Travel ME:** Clinical Phonocardiography and External Pulse Recording. Chicago, Year Book Medical Publishers, 1972, p 120

TEMPORARY TRANSVENOUS PACING AFTER MITRAL VALVE SURGERY

In connection with the recent article of Ritchie et al.[1] we recently saw a patient with class III symptoms of congestive heart failure, 3+ mitral regurgitation and normal coronary

arteries who underwent mitral valve replacement. Histologically, she had findings of myxomatous degeneration of the mitral valve. Her postoperative course was complicated by refractory ventricular tachycardia. Despite the use of massive doses of lidocaine, quinidine and procainamide hydrochloride, she continued to have recurrent ventricular tachycardia. After the insertion of a temporary transvenous pacemaker and overdrive suppression, she had no further rhythm problems. She was maintained on her pacemaker for 4 days and then successfully weaned from it. She continued to have infrequent ventricular ectopic beats.

Whether the refractory ventricular tachycardia and fibrillation are peculiar to patients with myxomatous degeneration of their valve or, in our patient's case, related to the trauma of surgery, is unclear. We believe, however, that prompt insertion of a temporary transvenous pacemaker is warranted in postoperative patients with refractory ventricular tachycardia and fibrillation.

Gary R. Cooper, MD
Cardiovascular Lab
Alachua General Hospital
Gainesville, Florida

Reference

1. **Ritchie JL, Hammarmeister KE, Kennedy JW, et al:** Refractory ventricular tachycardia and fibrillation in a patient with the prolapsing mitral leaflet syndrome: successful control with overdrive pacing. Am J Cardiol 37:314–316, 1976

BOOKS RECEIVED

Advances in Cardiology, Volume 16, Electrocardiology. Physiological, Pathophysiological and Diagnostical Research, edited by Hubert Abel. Basel, S. Karger, 1975, 568 pages, $51.75

Clinical Exercising Testing, by Norman L. Jones, MD, E. J. Moran Campbell, MD, PhD, Richard H. T. Edwards, BSc, PhD and Denis G. Robertson, FRACP. Toronto, W. B. Saunders, 1975, 214 pages, $15.50

Coronary Angiography and Angina Pectoris. Symposium of the European Society of Cardiology, edited by P. R. Lichtlen. Georg Thieme Publishers, 1976, 400 pages, $26.00

The Electrocardiogram. A Self-Study Course in Clinical Electrocardiography, by Emanuel Stein, LLB, MD. Philadelphia, W. B. Saunders, 1976, 405 pages, available with 10 C-60 sound cassettes, $14.00 (book only), $85.00 (tapes only), $99.00 (book and tapes)

Lipoprotein Metabolism, edited by Heiner Greten. New York Springer-Verlag, 1976, 162 pages, $11.50

Monographs on Atherosclerosis, Volume 7, Primate Atherosclerosis, edited by David Kritchevsky and O. J. Pollak. Basel S. Karger, 1976, 101 pages, $20.00

The Nervous System in Arterial Hypertension, edited by Steve Julius, MD, ScD and Murray D. Esler, MBBS, PhD. Springfield III, Charles C Thomas, 1976, 476 pages, $37.50

Systemic Effects of Antihypertensive Agents, edited by Mohinder P. Sambhi, MD, PhD. New York, Symposia Specialists 1976, 616 pages, $21.50

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

OCT. 1–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Leonard S. Dreifus, FACC, director. University City Holiday Inn, Philadelphia, Pa.

OCT. 1–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Borys Surawicz, FACC and Paul L. McHenry, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

OCT. 11–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Alberto Benchimol, FACC, director. Safari Resort Hotel, Scottsdale, Ariz.

OCT. 12–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, Calif.

OCT. 19–21 — **Ischemic Heart Disease: Current Concepts.** William J. Grace, FACC, James T. Mazzara, FACC and Richard J. Kennedy, FACC, directors. St. Vincent's Hospital and Medical Center of New York, New York, N.Y.

OCT. 21–23 — **New Techniques and Concepts in Cardiology: Exercise Stress, Exercise Testing and Cardiac Rehabilitation.** Stephen E. Epstein, FACC, director. The Washington Hilton Hotel, Washington, D.C.

OCT. 27–29 — **Cardiac Pacing.** Doris J. W. Escher, FACC and Seymour Furman, FACC, directors. New York Hilton Hotel, New York, N. Y.

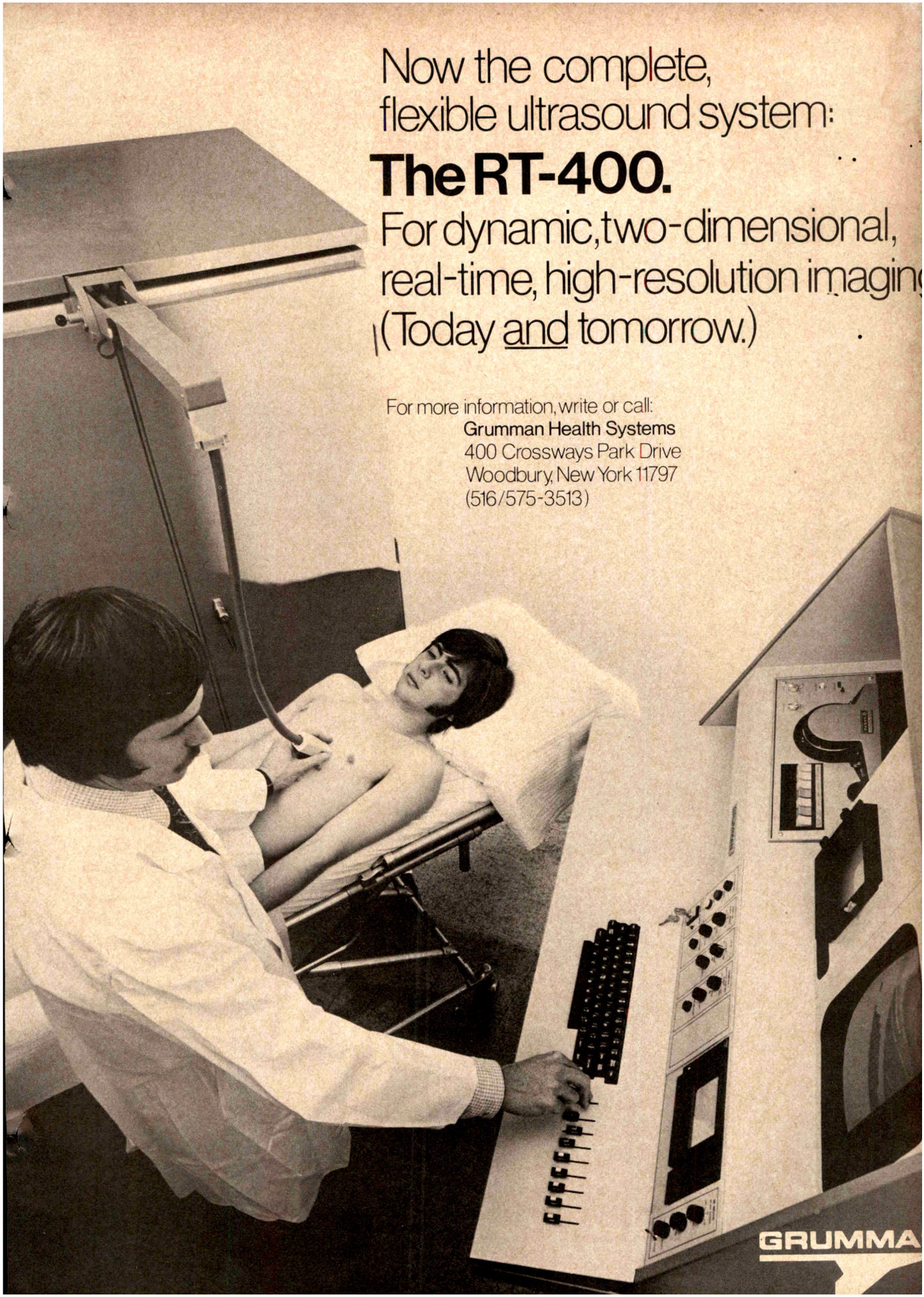
NOV. 27–29 — **Advances in Heart Disease—1977.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, Calif.

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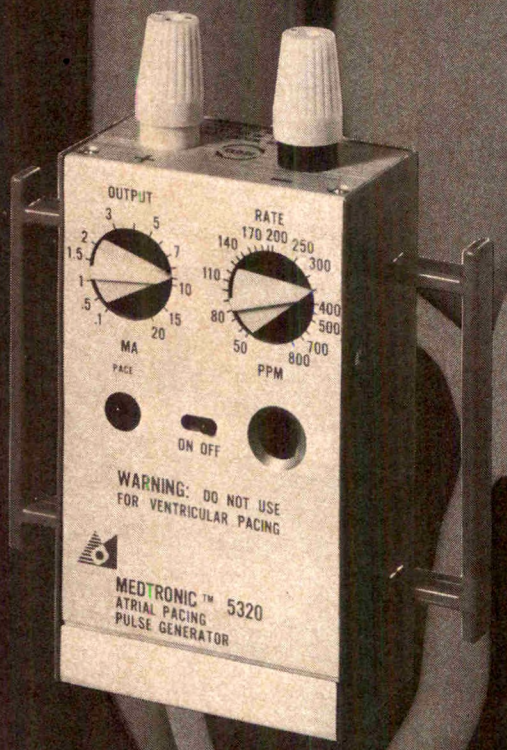
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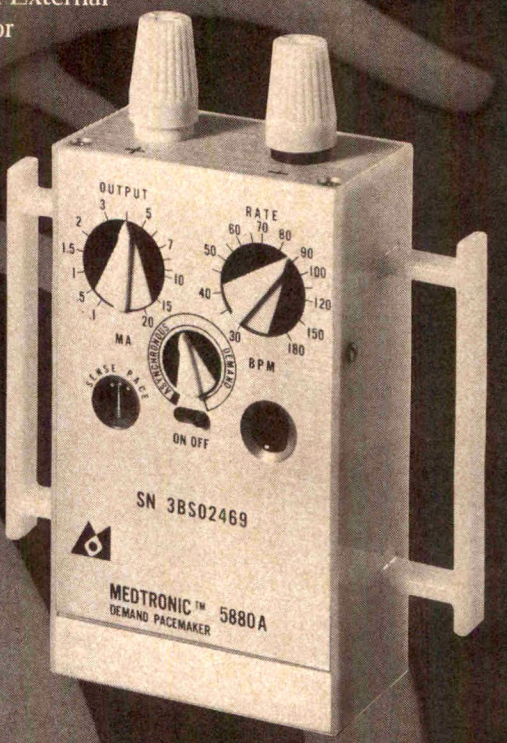
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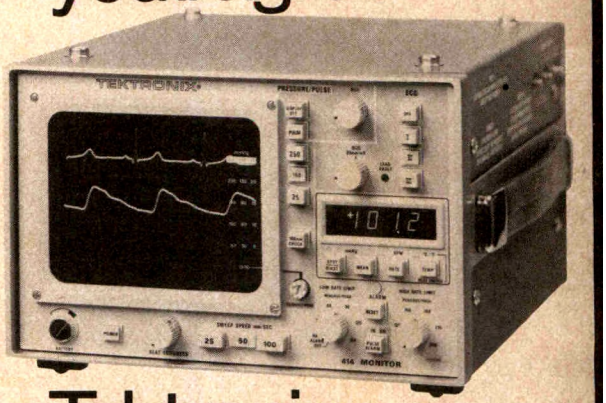
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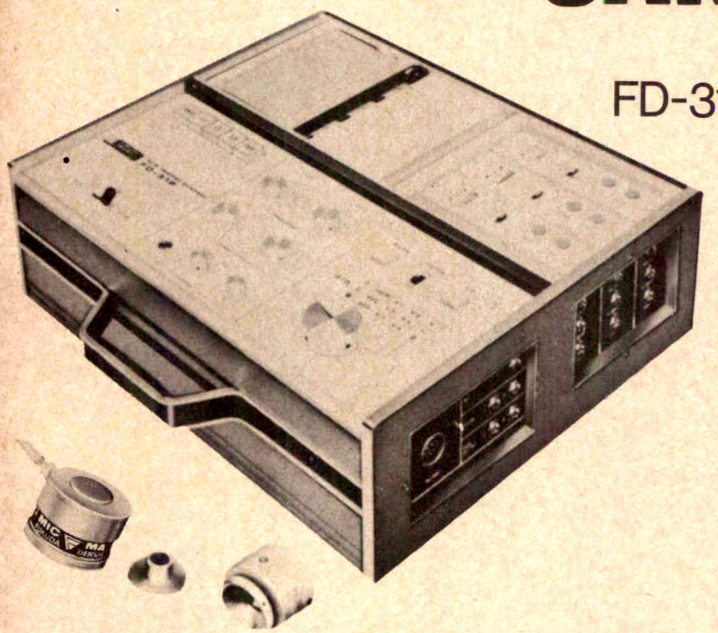
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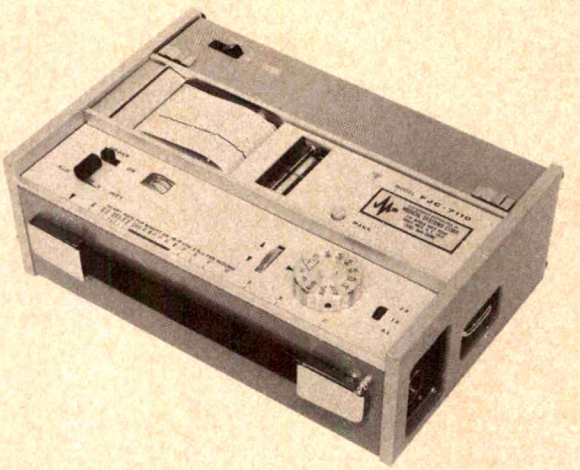
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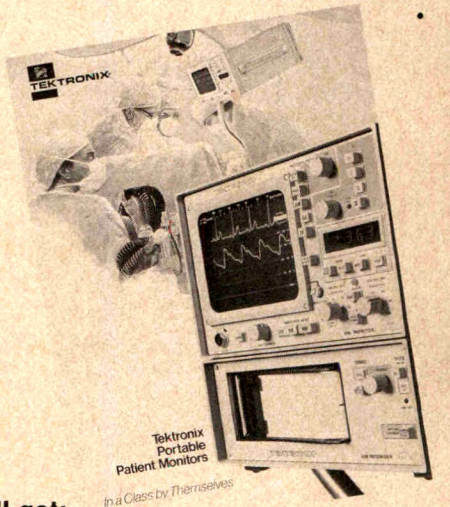
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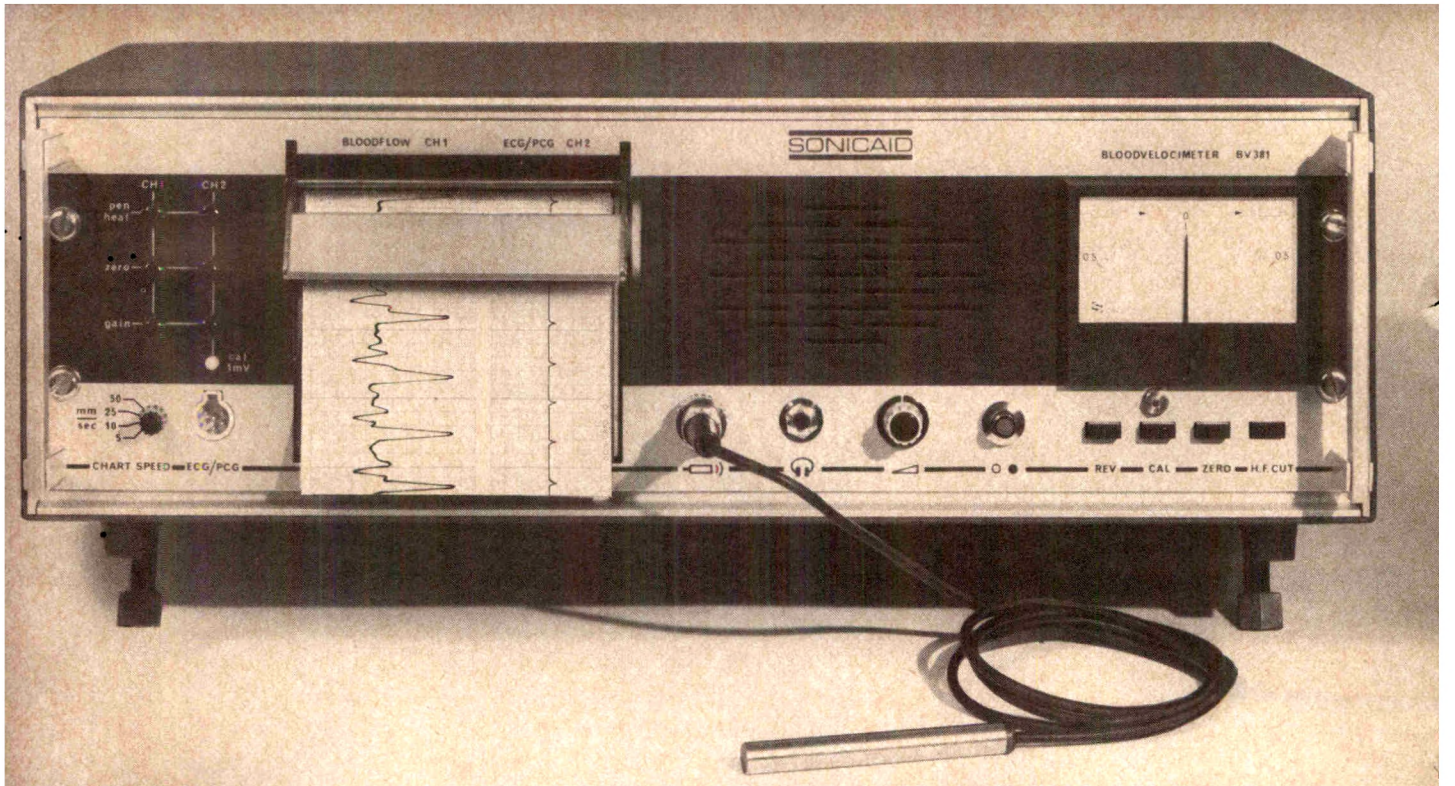
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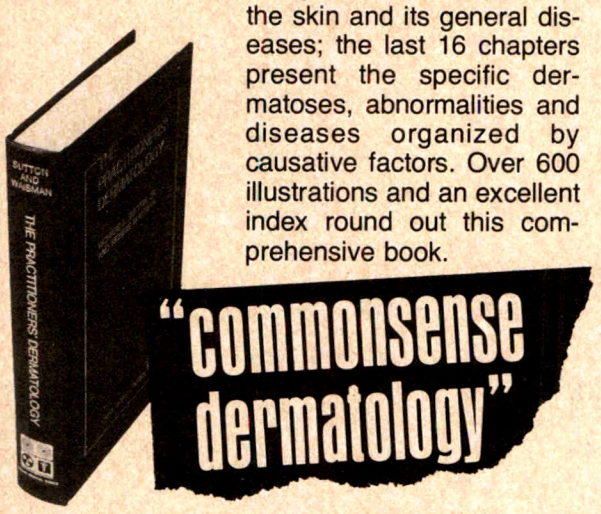
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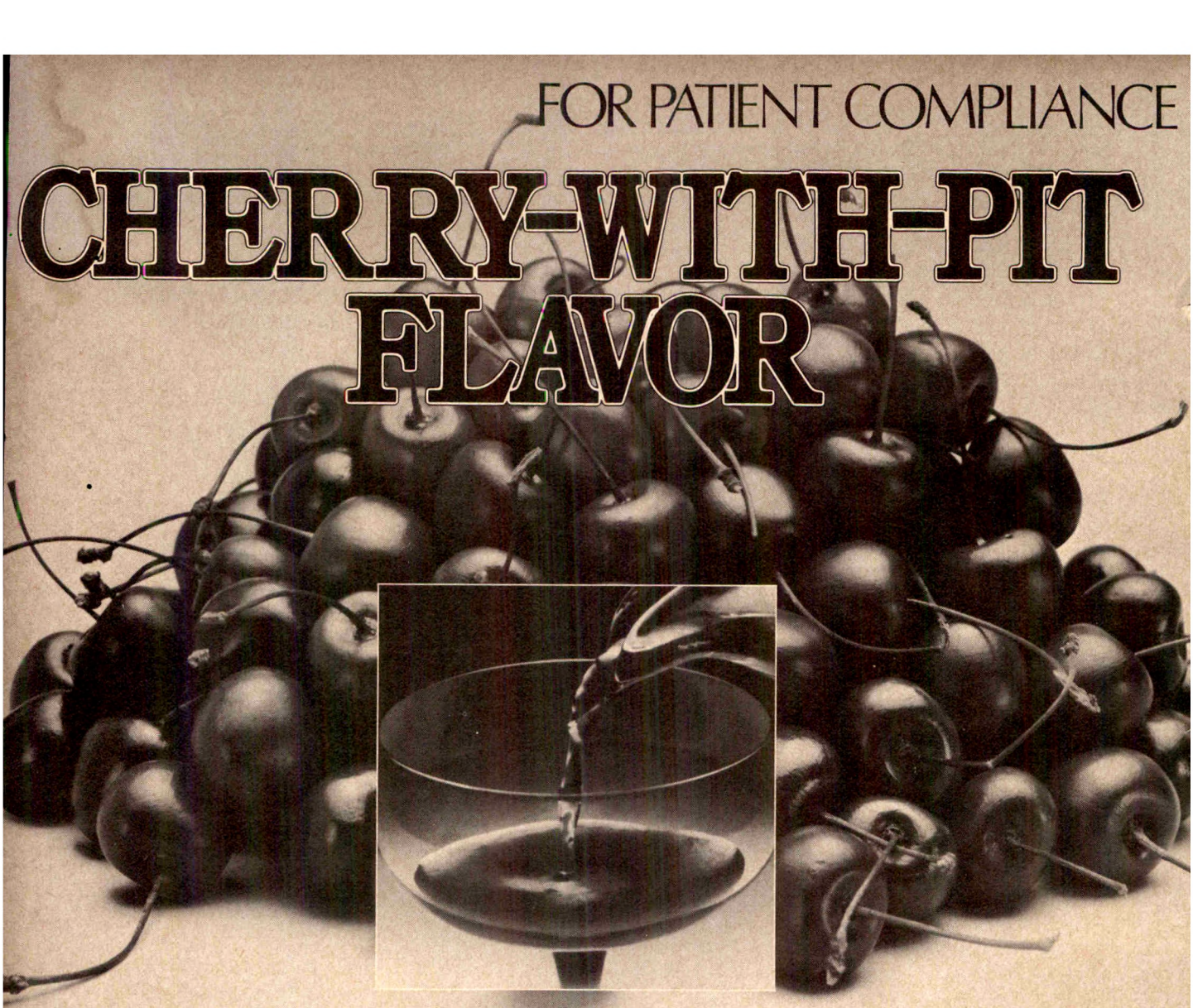
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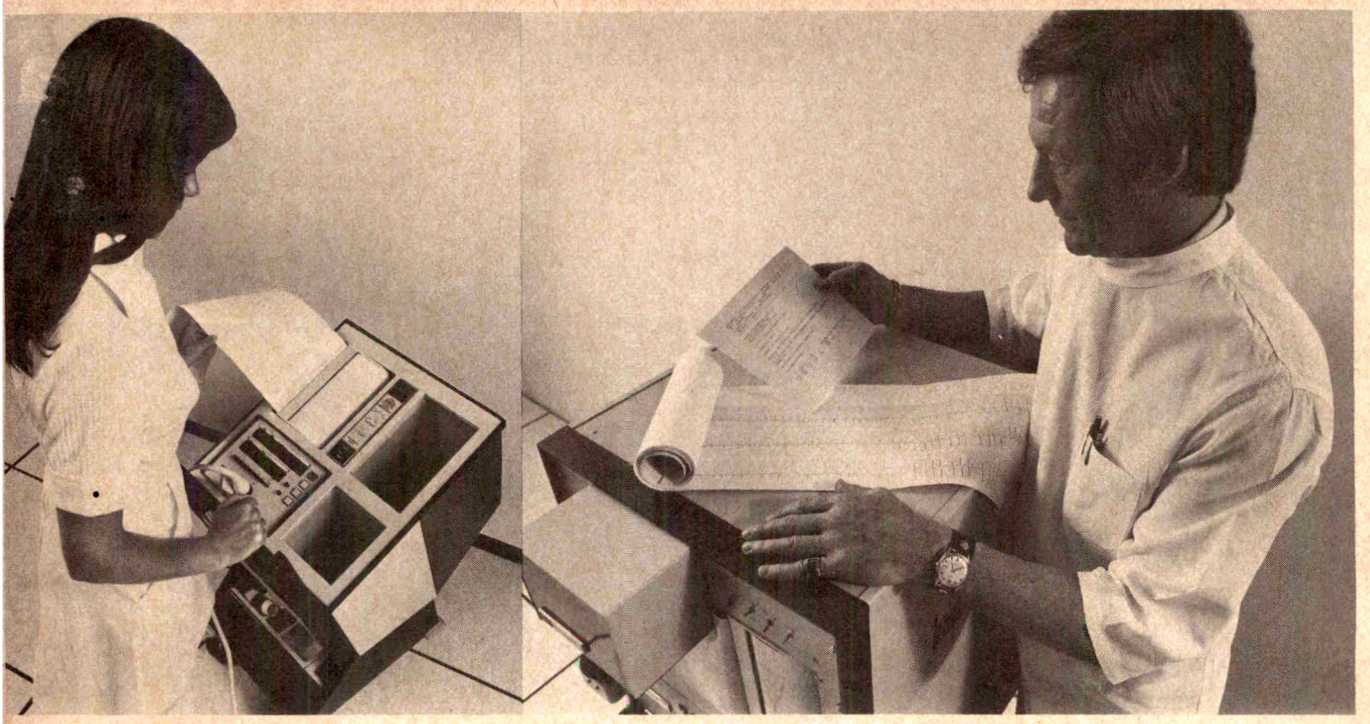
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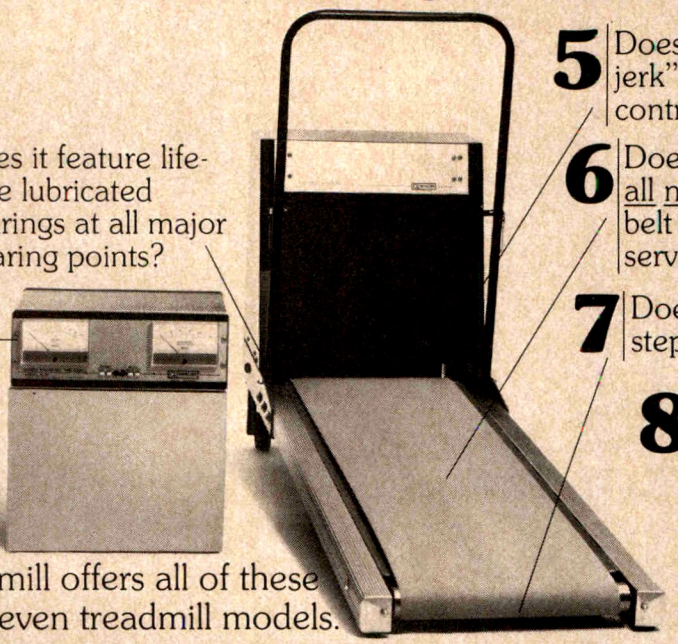
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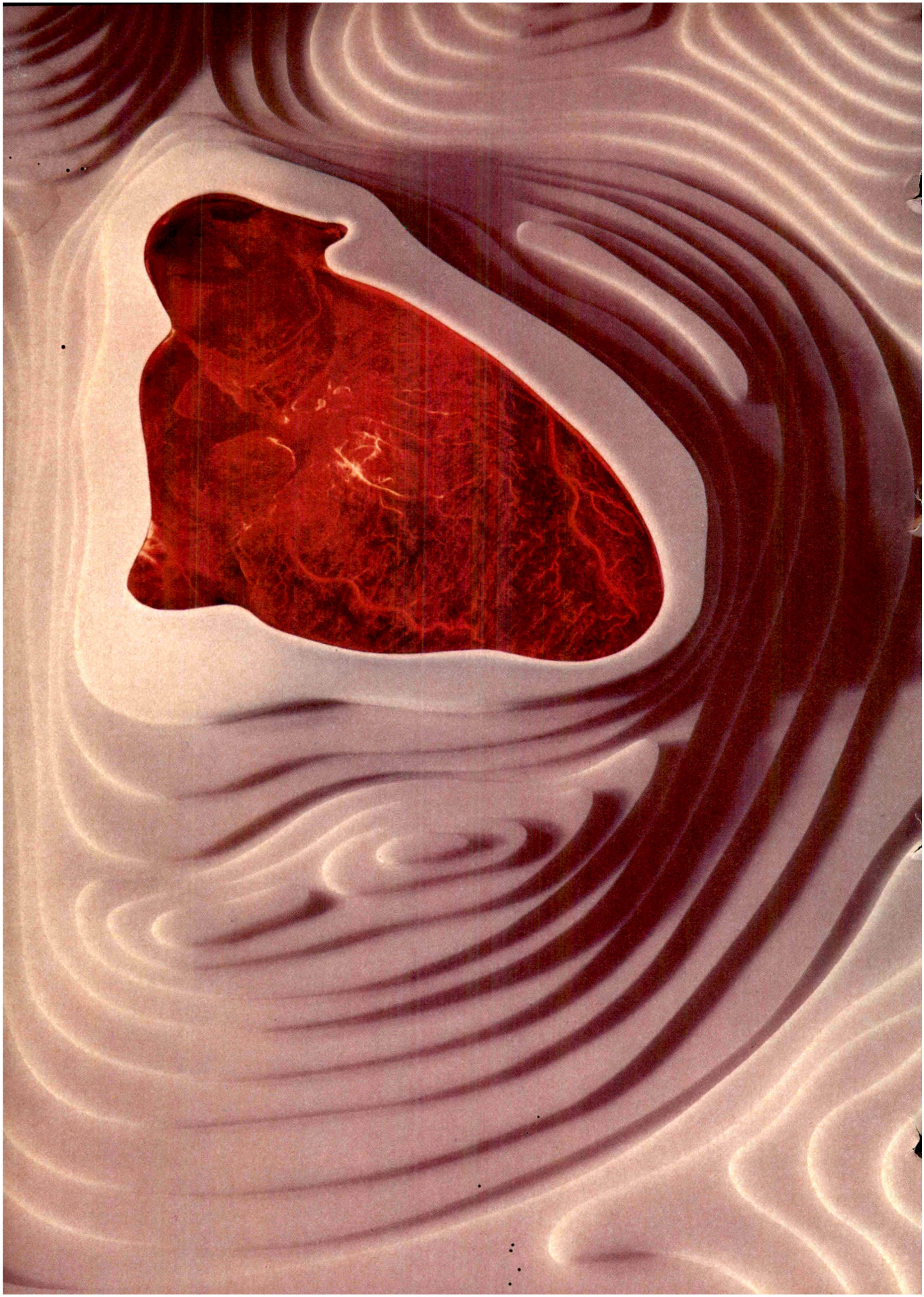
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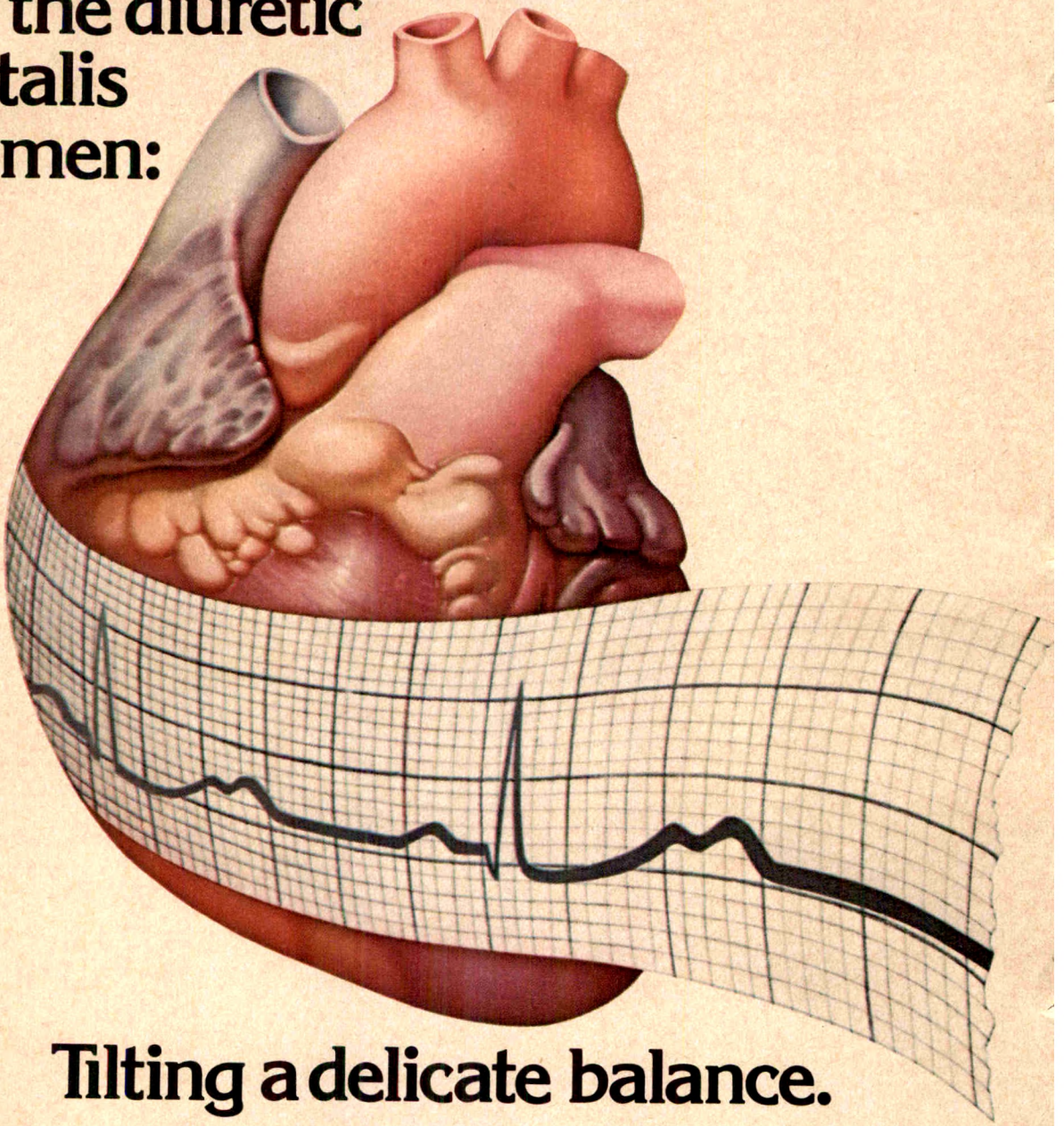
* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: Possibly effective: For the management, prophylaxis or treatment of anginal attacks. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy, hypotension.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdoses may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12-hour intervals.

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Certain diuretics such as thiazides, furosemide, and ethacrynic acid may remove potassium and the resulting potassium deficit can rapidly trigger arrhythmias in the digitalized patient. Of course, potassium supplements should not be administered with any potassium-sparing diuretics such as spironolactone and triamterene.

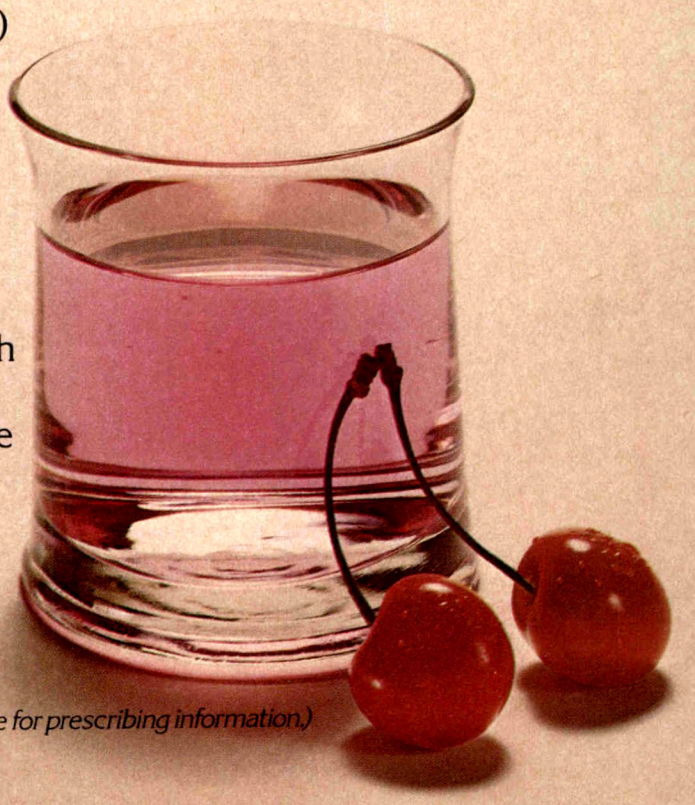
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■ One tablespoon (15 ml.) provides 40 mEq. each of potassium and chloride...nearly twice the potassium content of most single effervescent tablets or packets of powder.

■ Pleasant Cherry Flavor: One tablespoon (15 ml.) mixed with six fluid ounces of water or other liquid, few palatability problems are encountered. Kaon-CL 20% must be diluted before administration to avoid gastrointestinal irritation.



(See brief summary on following page for prescribing information.)

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Kaon-CL 20%™ (potassium chloride) Sugar-Free.
Description: Each 15 ml (tablespoonful) supplies 40 mEq each of potassium and chloride (as potassium chloride, 3 g) with saccharin and flavoring. Alcohol 5%.
Indications: Kaon-CL 20% is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL 20% is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.
Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).
Warnings: Do not administer full strength. Kaon-CL 20% will cause gastrointestinal irritation if administered undiluted. For details regarding adequate dilution, see Dosage and Administration.
In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.
Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation.
Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.
Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.
Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.
The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).
Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.
Dosage and Administration: Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.
One tablespoonful (15 ml) in six fluid ounces or more of water provides 40 mEq of potassium chloride.
One tablespoonful twice a day in six or more fluid ounces of water or other liquid provides 80 mEq potassium chloride.
Caution: Federal law prohibits dispensing without prescription.

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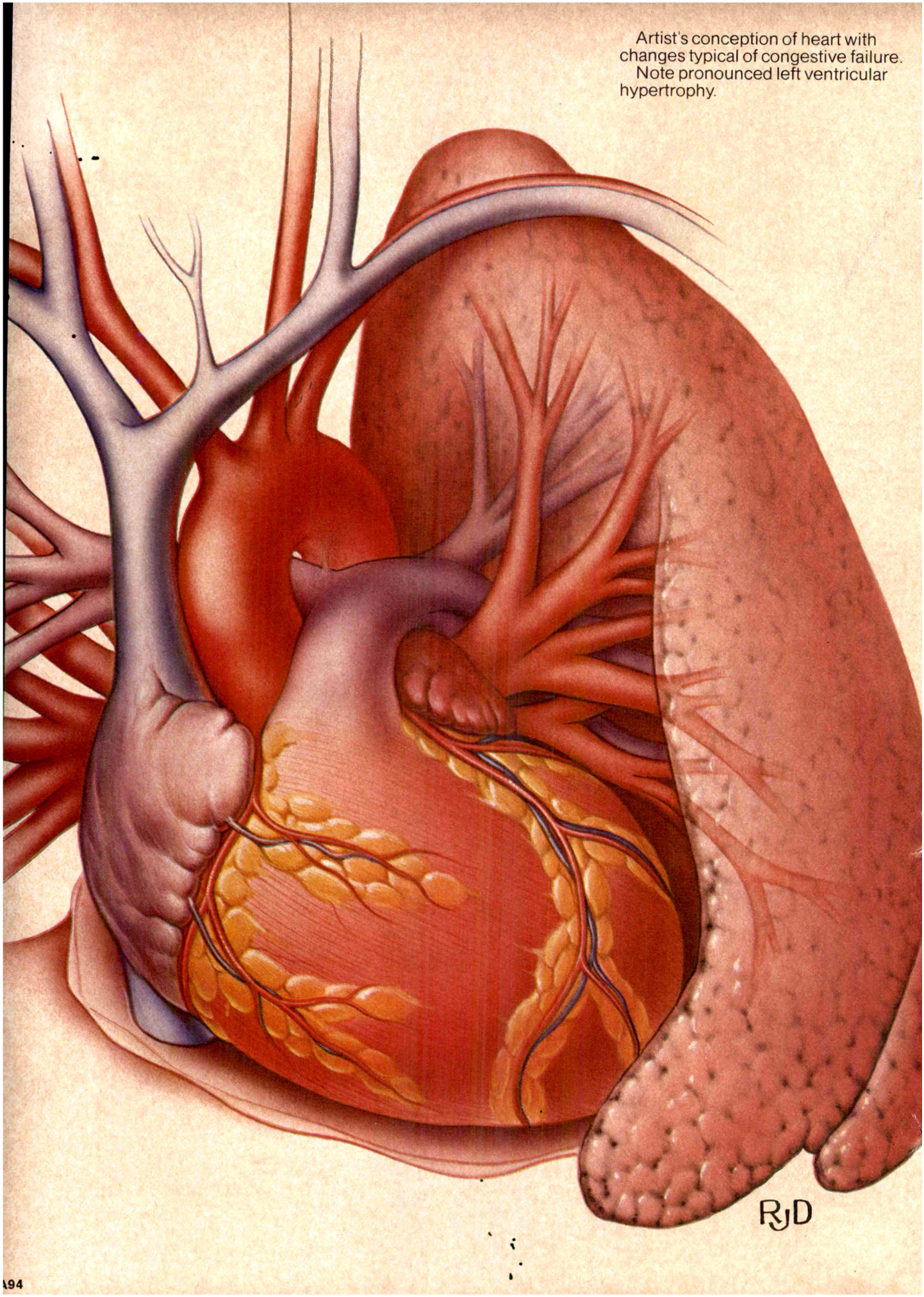
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Artist's conception of heart with changes typical of congestive failure. Note pronounced left ventricular hypertrophy.

In congestive heart failure...

aldosteronism promotes edema. "The hyperaldosteronism present in the majority of patients with congestive heart failure...explains the low sodium excretion in urine, sweat, and saliva. Ultimately, of course, this retention of salt and water leads to edema."[1]

Aldactone (spironolactone) combats aldosteronism... promotes diuresis.

"By administering spironolactone [Aldactone] over, say, three or four weeks, one may actually induce a greater sodium and water loss than with more powerful natriuretic agents. . . ."[2]

Effective diuresis in edema of congestive heart failure

Aldactone® (spironolactone) 25-mg. tablets

- Produces gradual, positive, sustained diuresis, usually without causing acute volume depletion, and without rebound fluid retention.
- Helps prevent potassium loss which may contribute to arrhythmias and digitalis toxicity.

See next page for brief summary of prescribing information.

In congestive heart failure

Aldactone®

(spironolactone)

25-mg. tablets

Indications—Essential hypertension; edema of congestive heart failure, cirrhosis of the liver, the nephrotic syndrome and idiopathic edema. Some patients with malignant effusions may benefit from Aldactone (spironolactone), particularly when given with a thiazide diuretic.

Contraindications—Acute renal insufficiency, rapidly progressing impairment of renal function, anuria and hyperkalemia.

Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

In a 78-week chronic toxicity study, rats were given daily oral doses of spironolactone approximately 30, 90 and 300 times the usual daily human therapeutic dose (100 mg. per day). The results of this study demonstrated a dose-related, statistically significant increase in the occurrence of benign adenomas of the testes and thyroid gland. Similar findings have not been demonstrated in other animal studies. In view of the marked differences in spironolactone metabolism by the rat and by man, the relationship of this finding to the possible development of tumors in humans is unknown.

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially with preexisting renal impairment. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it potentiates their action. The physician should be alert to the possible onset of gynecomastia.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are usually reversible. In rare instances gynecomastia may persist.

Dosage and Administration—**For essential hypertension in adults** the initial daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since the maximal response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema in adults initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will often be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be required (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should usually be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For children the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

References:

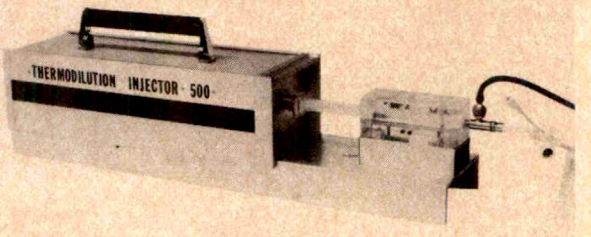
1. Genest, J., and Nowar, T.: Clinician: Congestive Heart Failure, Medcom® Learning Systems, New York, Medical Communications, Inc., 1972, pp. 42-49.
2. Laragh, J. H.: Hosp. Pract. 5:43-50 (Nov.) 1970.

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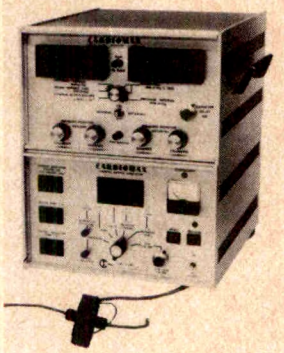
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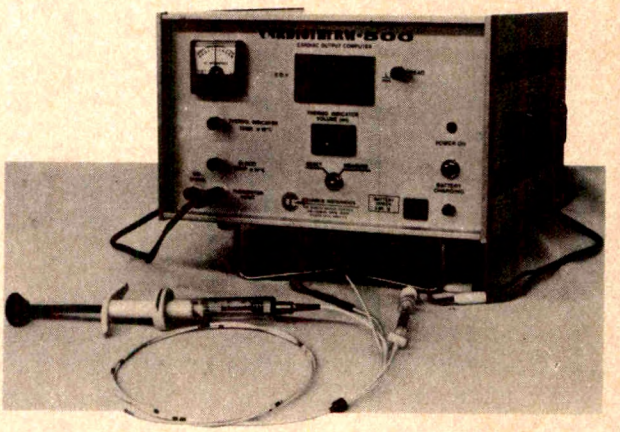


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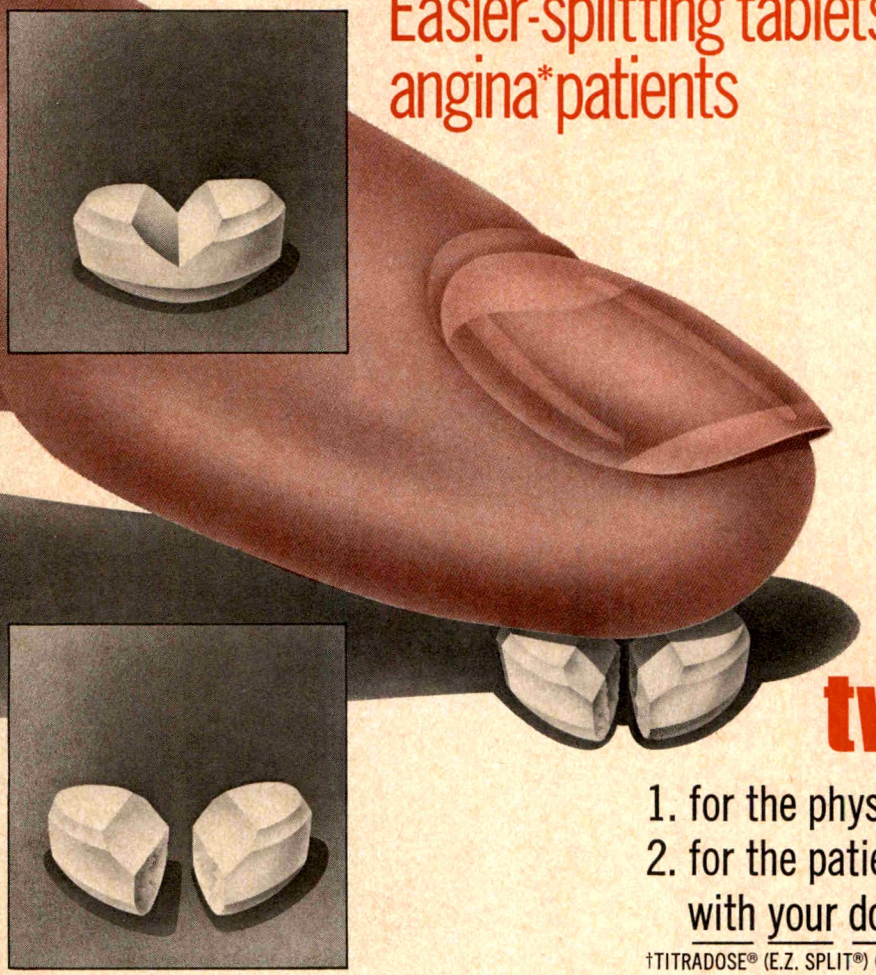
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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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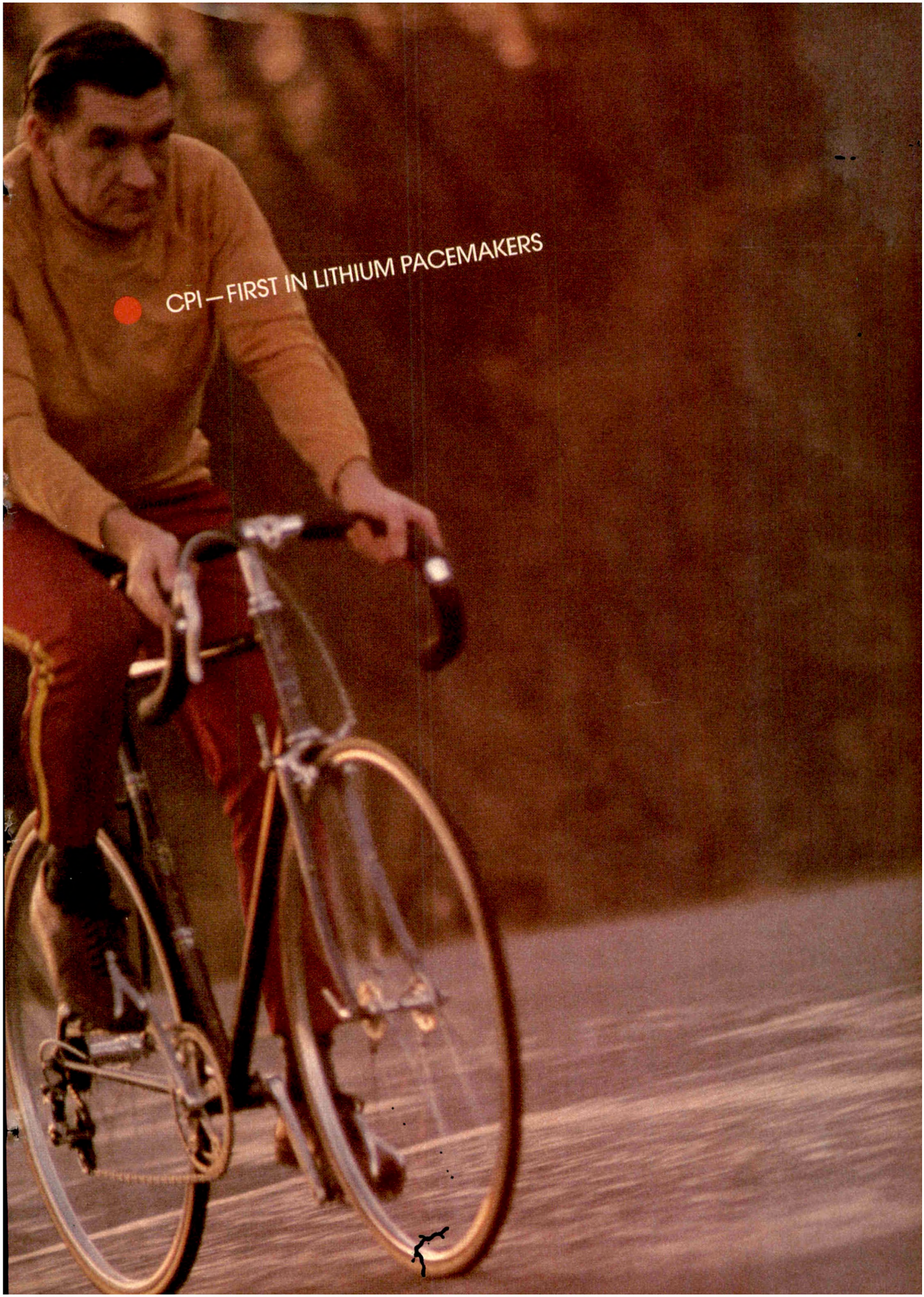


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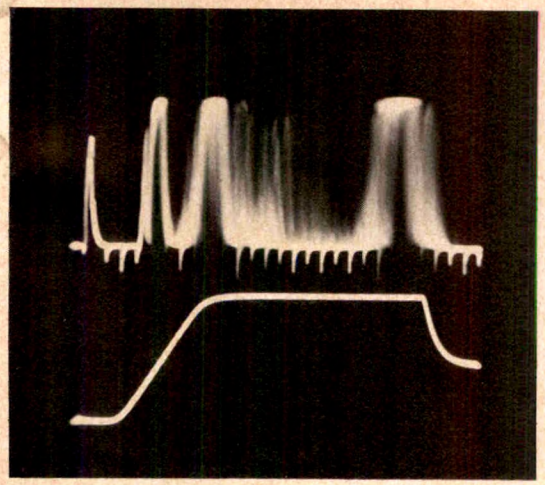
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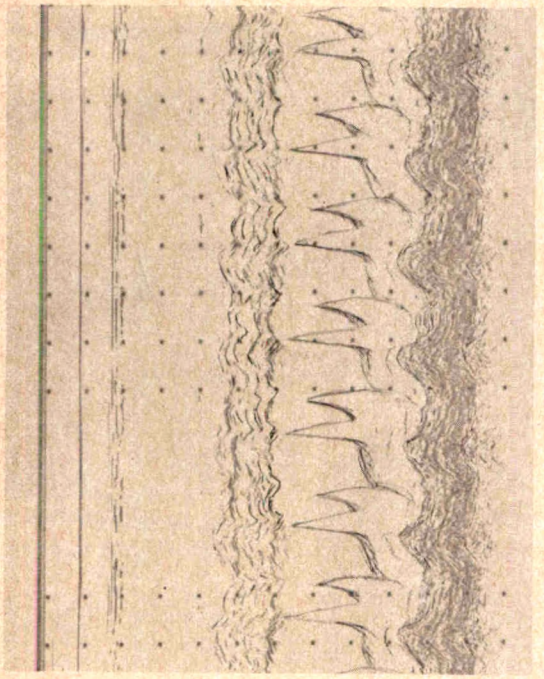
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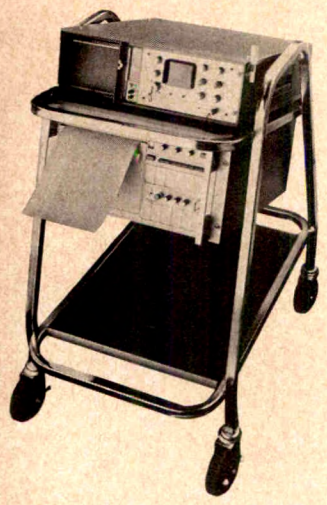
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Improve patient compliance by prescribing the KCl they need...in a way they'll like.



CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.

WARNINGS: Do not use excessively.

PRECAUTIONS:

PATIENTS SHOULD BE CAUTIONED TO ADHERE TO DILUTION INSTRUCTIONS.

ADVERSE REACTIONS: Potassium intoxication indicated by listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac depression, arrhythmias, arrest and heartblock. Vomiting, nausea, abdominal discomfort and diarrhea may occur.

145-4

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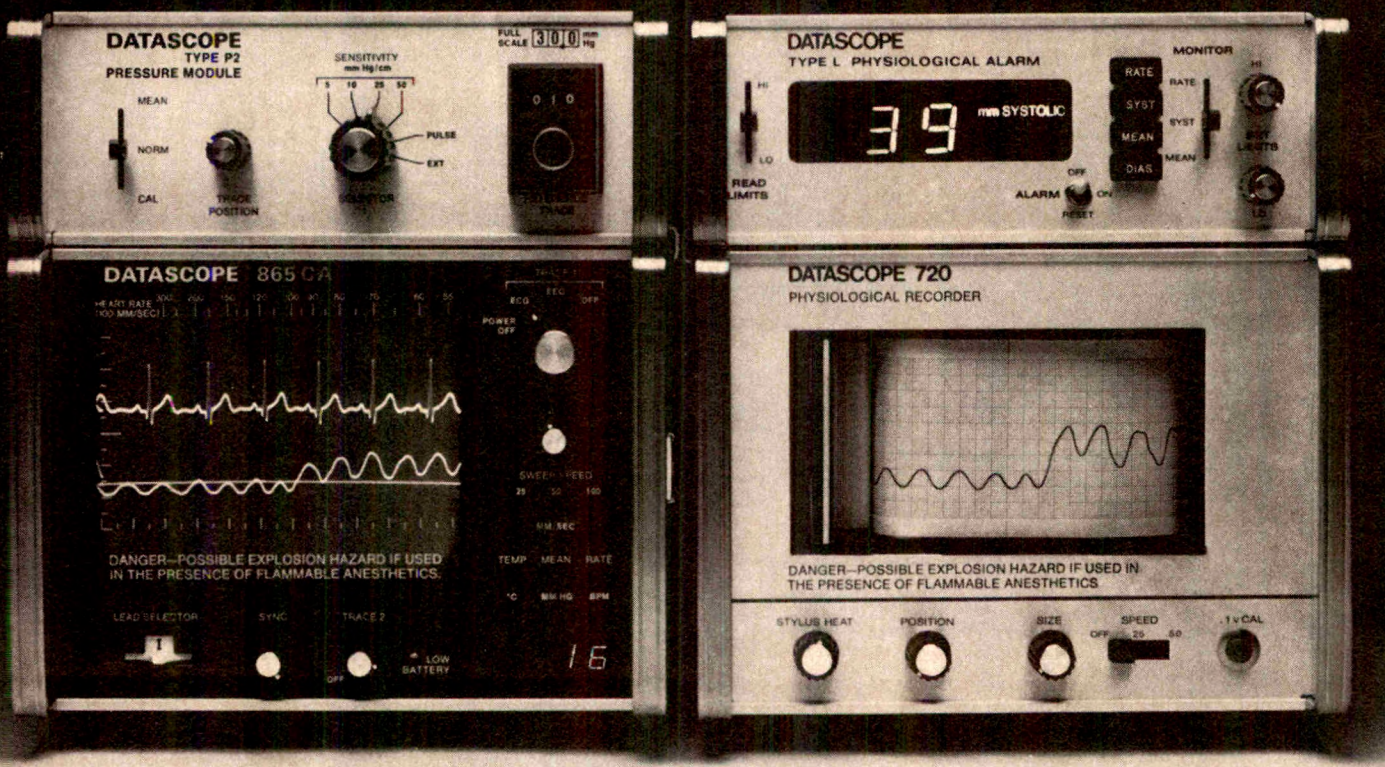
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And it's portable. You can move it where you need it, when you need it.

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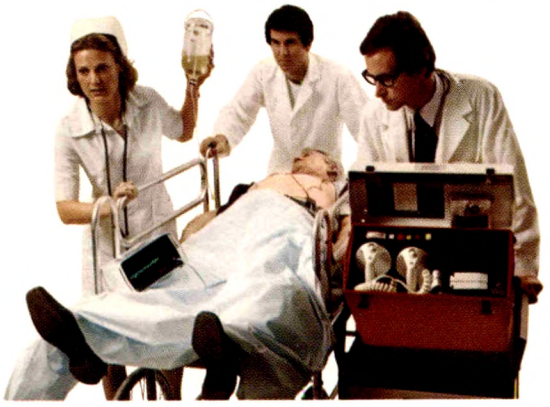
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For more information on the Datascope Wedge Pressure Group, write: Datascope Corp., 580 Winters Ave., Paramus, N.J. 07652.

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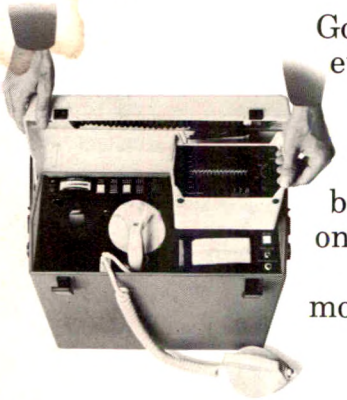
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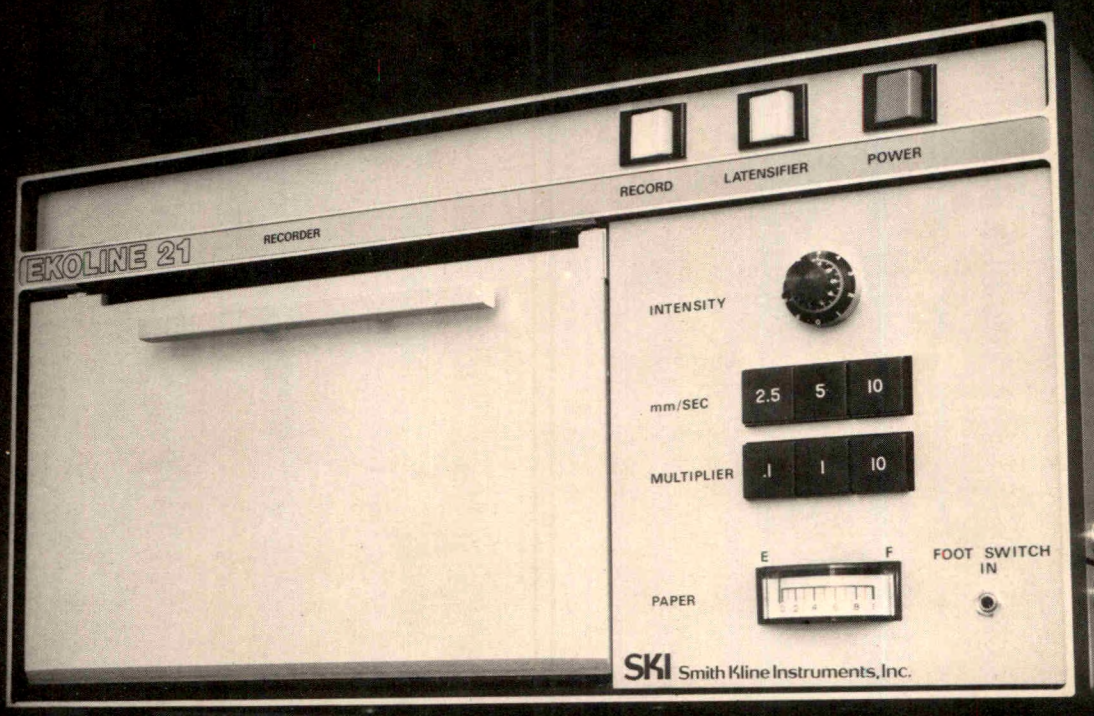
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If you would like more details about the new Ekoline 21 and the SKI Echo System, call or write: Smith Kline Instruments, Inc., Dept. U, 880 W. Maude Avenue, Sunnyvale, CA 94086. (408) 732-6000.

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For the special needs of patients with hard, dry stools

Hard, dry stools hurt, and may be hazardous by causing straining. SENOKOT S Tablets offer comfortable relief by softening the stool *and* stimulating its movement.

Provides standardized senna concentrate, a clinically established laxative of choice
Standardized senna concentrate is a gentle, effective neuroperistaltic stimulant with documented effectiveness in thousands of patients. Its virtually colon-specific, gentle, predictable action is generally free of side effects at proper dosage levels.

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DSS in SENOKOT S Tablets complements the laxative effect of standardized senna concentrate by "moistening" and softening the stool for smoother and easier passage.

Comfortable overnight action
With DSS and standardized senna concentrate, SENOKOT S Tablets provide *both* softness and stimulation for constipated patients with hard, dry stools. Taken at bedtime SENOKOT S Tablets usually induce predictable, comfortable evacuation the next morning.

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Senokot® S tablets

(standardized senna concentrate and dioctyl sodium sulfosuccinate)

the "S" stands for softener





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NOVEMBER 23, 1976

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Clinical Studies

Symposium on Advances in Cardiovascular Nuclear Medicine

Symposium on Hypertension. Part III

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Hypertension

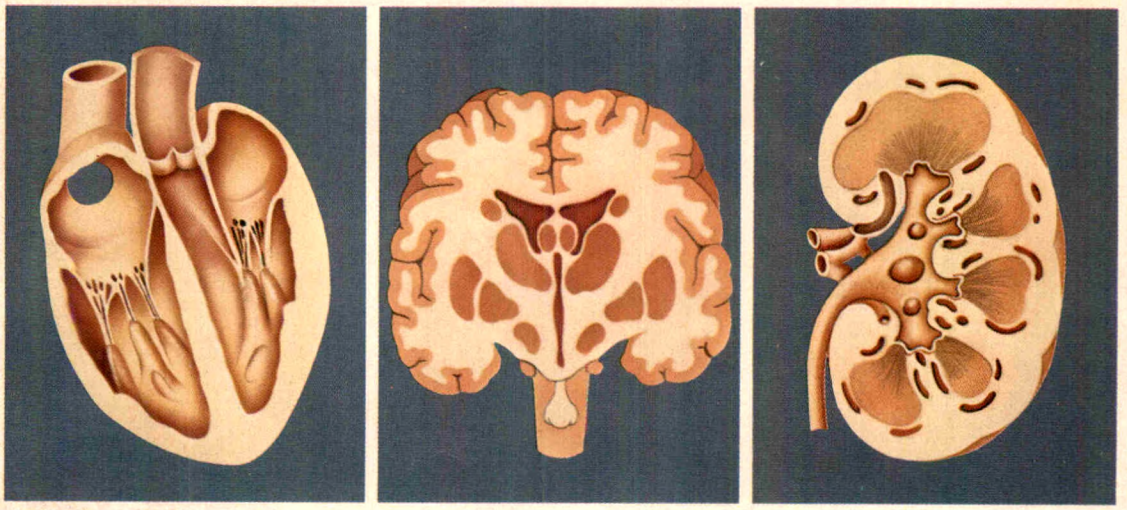
An important new indication for

Inderal®

Brand of

propranolol hydrochloride

Tablets 10 mg, 40 mg, 80 mg



Hypertension: a new indication for Inderal

Inderal (propranolol hydrochloride) is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. Inderal is not indicated for treatment of hypertensive emergencies.

Actions of Inderal

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Mechanism of antihypertensive effects

The mechanism of the antihypertensive effects of Inderal has not been established. Among the factors that may be involved are:

(1) decreased cardiac output,



(2) inhibition of renin release by the kidneys, and



(3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.



Inderal dosage must be individualized

■ The initial dose is 80 mg Inderal daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved.

■ The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required.

■ The time course of full blood pressure response is variable and may range from a few days to several weeks.

■ Inderal is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When Inderal is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

How Inderal is supplied

TABLETS

—Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000.
(See HOW SUPPLIED section information on following pages.)



Before prescribing Inderal for hypertension, please read the full prescribing information on the following two pages.

Ayerst

(For full product information, see package circular.)

INDERAL®
Brand of propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Additional carcinogenicity studies in rats and mice conforming to recently accepted protocols are nearing completion and no drug-related increase in tumors has been observed.

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS

Hypertension

INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis

The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL (propranolol hydrochloride) exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

Cardiac Arrhythmias

1.) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)

b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.

c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)

d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.

e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.

a) Ventricular tachycardias

With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*

b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL (propranolol hydrochloride) may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depress-

ing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL (propranolol hydrochloride) therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM *(e.g.,* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL (propranolol hydrochloride) may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects (fetal resorptions) have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

HYPERTENSION — *Dosage must be individualized.*

The initial dose is 80 mg INDERAL daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved. The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required. The time course of full blood pressure response is variable and may range from a few days to several weeks. INDERAL is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When INDERAL is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

ANGINA PECTORIS — *Dosage must be individualized.*

Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

ARRHYTHMIAS — 10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS — 20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA — *Preoperatively* — 60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

— *Management of inoperable tumor* — 30 mg daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA — ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE — DIGITALIZATION AND DIURETICS

HYPOTENSION — VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM — ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

(propranolol hydrochloride)

TABLETS

— Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0461-81) and 1,000 (NDC 0046-0461-91). Also in unit dose package of 100 (NDC 0046-0461-99).

— Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0464-81) and 1,000 (NDC 0046-0464-91). Also in unit dose package of 100 (NDC 0046-0464-99).

— Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0468-81) and 1,000 (NDC 0046-0468-91). Also in unit dose package of 100 (NDC 0046-0468-99).

INJECTABLE

— Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

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IN CONGESTIVE HEART FAILURE*

ADD

DYRENIUM®

(triamterene, SK&F CO.) Capsules, 50 mg. and 100 mg.

TO FUROSEMIDE

WHEN CONSERVATION OF POTASSIUM BALANCE IS DESIRED

'Dyrenium' helps the patient retain essential potassium stores even during the first critical days of vigorous therapy with potent diuretics and digitalis.

When used with another diuretic, 'Dyrenium' has an additive effect, so initial dosage of both agents should usually be reduced; careful supervision and dosage adjustment are required. K^+ supplements should not be given unless dosage adjustment fails to reduce excessive K^+ loss, hypokalemia develops, or dietary K^+ intake is markedly reduced. Hyperkalemia can occur, but it is rare in patients with normal renal function. Serum K^+ and BUN should be checked periodically, particularly in elderly patients, diabetics, or those with suspected or confirmed renal insufficiency.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

***Indications:** Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid-induced edema, idiopathic edema, edema due to secondary hyperaldosteronism, to increase diuresis in patients resistant to other diuretics alone.

Contraindications: Severe or progressive kidney disease or dysfunction (possible exception: nephrosis). Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity to the drug. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy only when essential to patient welfare.

Dyrenium (triamterene, SK&F) and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Do periodic hematologic studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.
Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).



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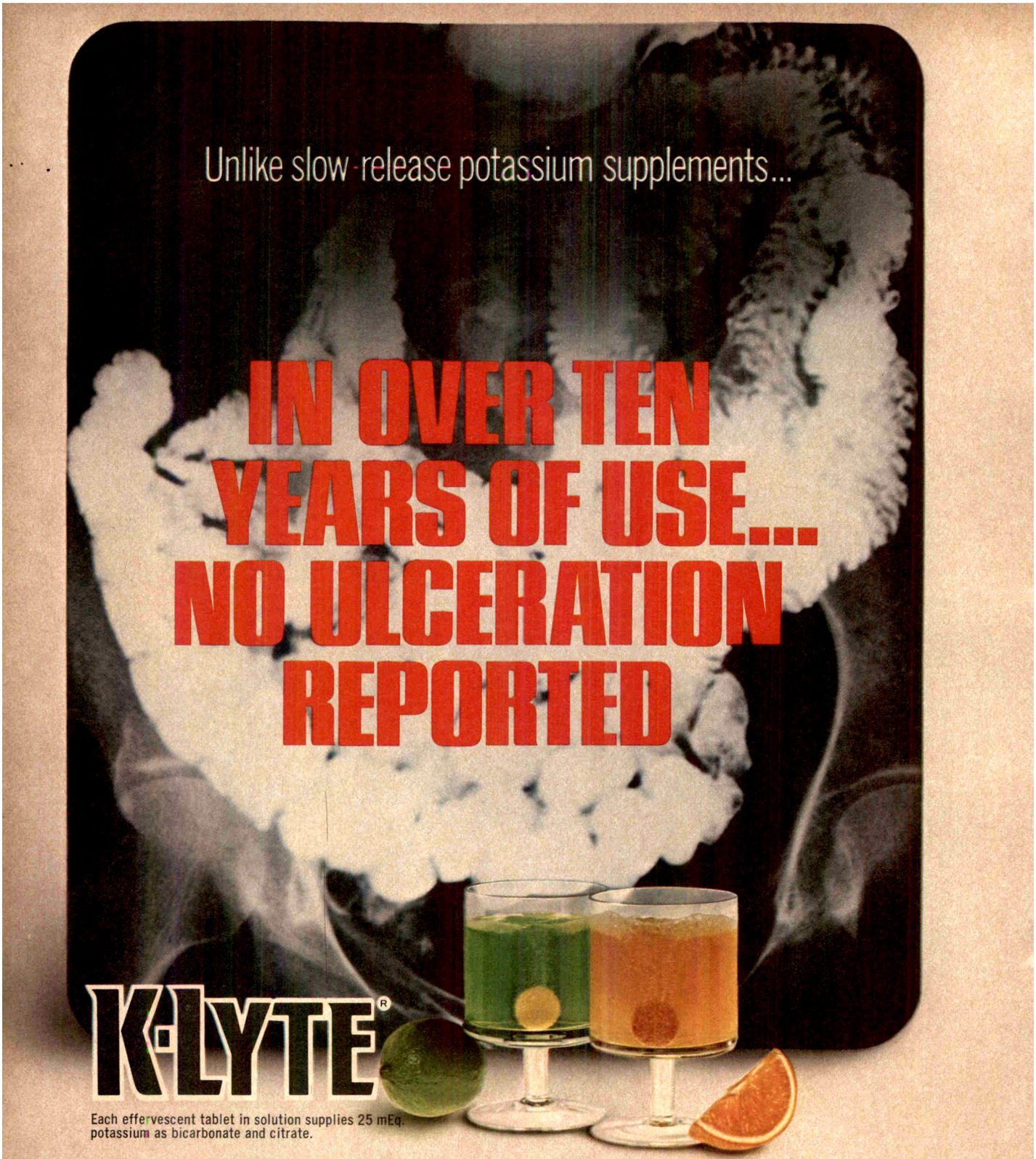
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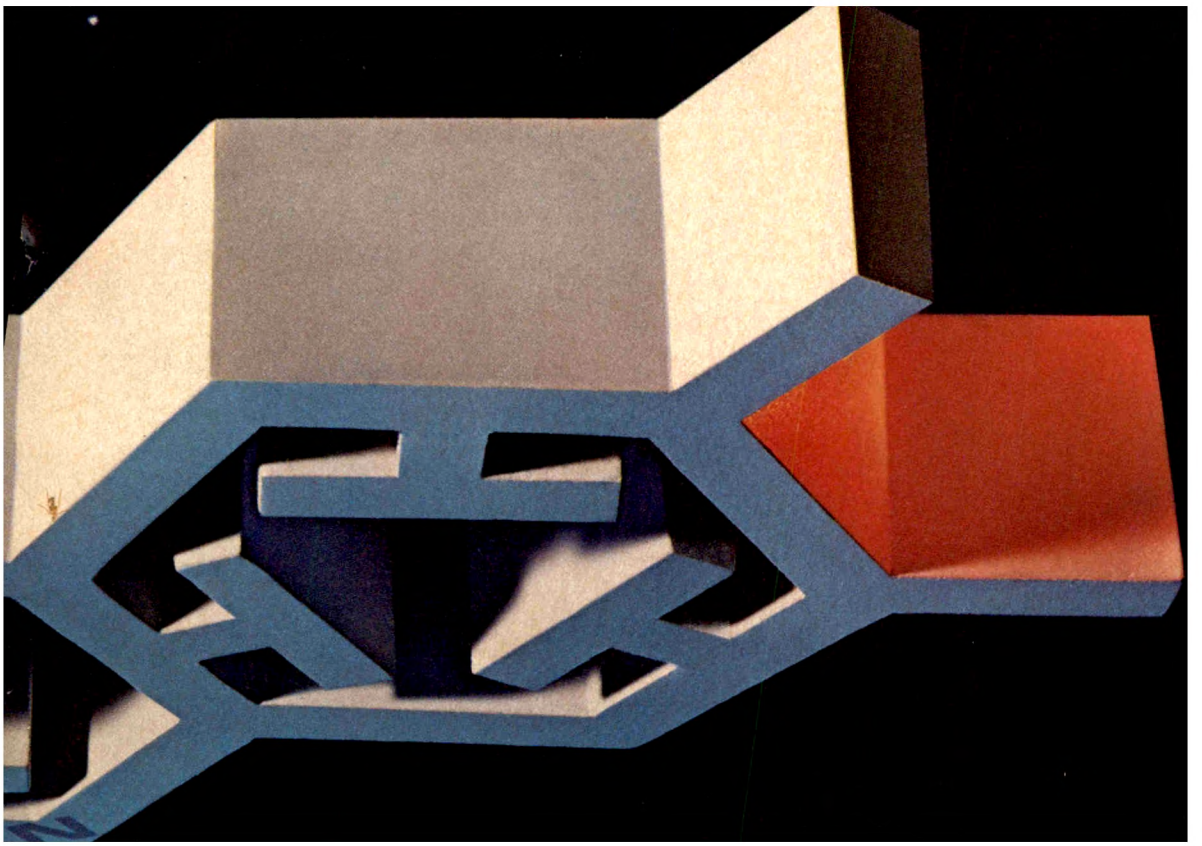
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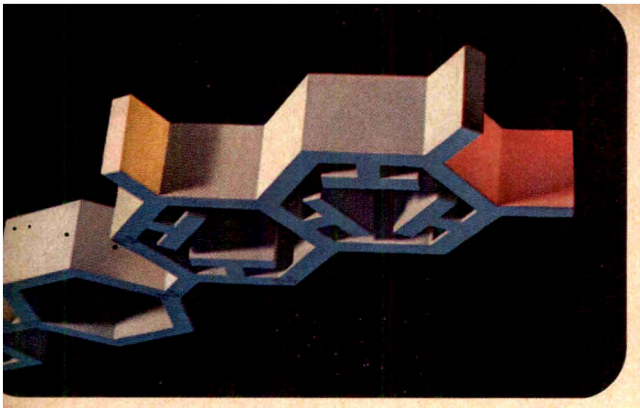
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- mild to moderate in activity
- effective in all grades of hypertension
- well suited for long-term therapy*
- no tolerance observed in long-term therapy*



The above is an artistic rendition of the molecular structure of prazosin.

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ELL SUITED FOR LONG-TERM THERAPY...
EW **MINIPRESS**® Capsules 1 mg., 2 mg., 5 mg.
(prazosin HCl)

Chemically unique vasodilator.

Mild to moderate in activity.

Effective in all grades of hypertension, either alone or in combination with a diuretic and/or other antihypertensive agent.

Direct action on the arterioles without clinically significant effects on cardiac output, renal blood flow or glomerular filtration rate. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.

No tolerance observed in long-term therapy in patients on continuous therapy for periods of up to 5 years.

Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.

Side effects most frequently experienced with Minipress in a series of 934 patients were: dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). A small percentage of patients have experienced orthostatic hypotension (3.4%) and syncope (1.3%). (For a more detailed description of orthostatic hypotension and syncope, see Warnings in Brief Summary before initiating therapy with Minipress.)

Starting dosage: 1 mg. t.i.d.

Usual maximum recommended dosage: 20 mg. daily, given in divided doses.

Available in 1-mg., 2-mg., and 5-mg. capsules.

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*
INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250.

More detailed information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC

NOVEMBER 23, 19

The American Journal of CARDIOLOGY

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CLINICAL STUDIES

677 **Acute Oral Testing for Determining Antiarrhythmic Drug Efficacy. I. Quinidine**

CHARLES E. GAUGHAN, BERNARD LOWN, JOSEPH LANIGAN, PANOS VOUKYDIS and HENRIQUE W. BESSER

Acute oral drug testing with quinidine was carried out in 18 patients with high grade ventricular arrhythmia, consisting of administering a single large dose of quinidine, monitoring heart rhythm by programmed trendscription and measuring blood drug levels at selected intervals to record peak drug action and dissipation of effect over a period of 3 hours. This method provides an effective way to determine if quinidine is effective or hazardous. In seven of nine patients receiving maintenance quinidine therapy this method predicted the result when exposure of arrhythmia was achieved by either maximal exercise stress or 24 hour monitoring.

685 **Undesirable Cardiac Arrhythmias Associated With Rate Hysteresis Pacemakers**

MARK E. THOMPSON and JAMES A. SHAVER

The development of serious cardiac arrhythmias in two patients with rate hysteresis pacemakers required replacement of their pulse generators. The hysteresis interval after a sensed signal may result in long pauses that predispose to ventricular arrhythmias. Such pacemakers should be reserved for patients with predominantly sinus rhythm and no ventricular excitability. A permanent demand pacemaker with external rate control may provide greater flexibility in managing arrhythmias in patients with frequent ectopic ventricular activity not easily controlled by antiarrhythmic agents.

689 **Propranolol-Induced Reduction of Signs of Ischemic Injury During Acute Myocardial Infarction**

HERMAN K. GOLD, ROBERT C. LEINBACH and PETER R. MAROKO

The intravenous administration of 3 to 10 mg of propranolol to 12 patients with acute anterior transmural myocardial infarction significantly reduced within 30 minutes the signs of myocardial ischemic injury without excessively depressing myocardial function. Significant improvement occurred in S-T segment changes, heart rate, mean arterial pressure, cardiac output, ischemic pain and ventricular arrhythmias. Such therapy can be safely used in the early hours after myocardial infarction, when patients are categorized hemodynamically before drug administration and those with impaired circulatory dynamics excluded.

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696 **Propranolol Therapy in Patients Undergoing Myocardial Revascularization**

ELLIS L. JONES, JOEL A. KAPLAN, EDWARD R. DORNEY, SPENCER B. KING, III, JOHN S. DOUGLAS, Jr. and CHARLES R. HATCHER, Jr.

In this series of 185 patients undergoing coronary bypass surgery, operative mortality was not significantly different among patients who received propranolol within 48 hours of myocardial revascularization (3 percent), those who never took it and those who discontinued it more than 48 hours before operation (4 percent). Because abrupt withdrawal of propranolol in patients with unstable angina may lead to acute myocardial infarction, gradual withdrawal of propranolol is recommended during the 48 hours before operation. If this is not possible, reduced doses may be given up to 10 hours before operation.

701 **Effect of Lithium on Cardiovascular Performance: Report on Extended Ambulatory Monitoring and Exercise Testing Before and During Lithium Therapy**

ARA G. TILKIAN, JOHN S. SCHROEDER, JOHN KAO and HERBERT HULTGREN

Long-term lithium therapy may precipitate or aggravate ventricular arrhythmias but apparently does not affect cardiovascular performance as assessed by treadmill exercise testing in 12 subjects receiving such treatment. Dosage must be adjusted in patients with heart disease according to the factors interfering with renal clearance of this drug, such as heart failure, salt restriction and long-term diuretic therapy. Careful follow-up and electrocardiographic monitoring are required if lithium is used in the presence of ventricular arrhythmias.

SYMPOSIUM ON ADVANCES IN CARDIOVASCULAR NUCLEAR MEDICINE

709 **Introduction**

HENRY N. WAGNER, Jr.

711 **Radioactive Tracers in Congenital Heart Disease**

SALVADOR TREVES and RUTH L. COLLINS-NAKAI

Advances in radionuclide angiocardiographic equipment and the development of ultrashort-lived radionuclides have improved the diagnostic capabilities and safety of this useful and nontraumatic radionuclear method of evaluating patients with congenital heart disease. Important applications are the detection, localization and quantification of intracardiac shunts, particularly in the evaluation of the newborn infant with cyanosis or respiratory distress syndrome and the patient who has had cardiovascular surgery.

722 **Clinical Appraisal of Current Nuclear and Other Noninvasive Cardiac Diagnostic Techniques**

ALFRED F. PARISI, DONALD W. TOW and ARTHUR A. SASAHARA

This review evaluates the current usefulness and limitations of the more important nuclear and other noninvasive diagnostic methods and their potential for solving problems in cardiovascular disease without escalating costs. These are particularly applicable to assessment of myocardial perfusion and myocardial function in coronary artery disease, identification and quantitation of cardiac valve disease and to recognition of pulmonary embolism without angiography.

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731 **Common Procedures for the Noninvasive Determination of Regional Myocardial Perfusion, Evaluation of Regional Wall Motion and Detection of Acute Infarction**

H. WILLIAM STRAUSS and BERTRAM PITT

Attention is directed to some of the physiologic factors controlling the distribution of radioactive tracers and the technical factors involved in their optimal recording and display. The procedures reviewed are the myocardial perfusion scan, both at rest and during stress; the recording of regional wall motion to evaluate ejection fraction and ventricular volumes and the size, shape and position of the cardiac chambers; and imaging of acute myocardial infarcts.

739 **Myocardial Perfusion Imaging and Gated Cardiac Blood Pool Scanning: Clinical Application**

BERTRAM PITT and H. WILLIAM STRAUSS

The increasing uses of myocardial perfusion imaging and gated cardiac blood pool scanning in clinical cardiology include the detection of myocardial infarction when other noninvasive tests are not diagnostic, and determination of the site and extent of the infarct and the effect of the infarct on left ventricular function, particularly in cardiogenic shock. Imaging with thallium-201 at rest and after exercise may be more sensitive than exercise electrocardiography in detecting ischemic heart disease. The combined tracers technique is of value in studying patients undergoing coronary bypass surgery and those with cardiomyopathy.

747 **The Nuclear Stethoscope: A Simple Device for Generation of Left Ventricular Volume Curves**

HENRY N. WAGNER, Jr., ROBERT WAKE, EDWARD NICOLOFF and T. K. NATARAJAN

This elegant first generational prototype of a nuclear stethoscope simplifies the recording of a time-dependent image of the rate of filling and emptying of the left ventricle. The knotty problems of calibration, correcting for background, and proper positioning of the detector must be solved before its full potential can be realized in the measurement of time intervals, ejection fraction and absolute ventricular volumes.

751 **Pathophysiologic Studies of the Pulmonary and Coronary Circulations in Man**

ATTILIO MASERI

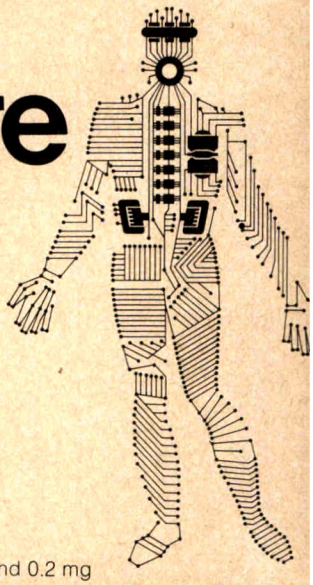
Nuclear medicine techniques show pulmonary blood flow is about 10 percent of the total blood volume in normal man and pulmonary blood volume is unchanged in patients with acute or chronic left atrial hypertension and in normal persons during expansion of total blood volume. Regional myocardial perfusion studies with xenon-133 reveal localized areas of ischemia distal to stenotic lesions even in resting patients. More severe ischemia is detected during angina produced by pacing. During attacks of variant angina, imaging with thallium-21 reveals cold areas suggesting transmural ischemia corresponding to the site of S-T elevation.

Continued on page A17


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This paper attempts to provide an informative matrix for discussion and decision making concerning the organization and planning of cardiovascular nuclear medicine units that will not be made obsolete by the rapid rate of technologic advances in this growing field. Close cooperation between cardiologists and nuclear medicine physicians, recognition of the special needs of patients with acute and chronic cardiovascular disorders and the inclusion of one or more satellite units in addition to the central nuclear medical facility are some basic considerations for proper planning.

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Mainly as a direct consequence of the mechanical stress placed on the heart and blood vessels, hypertension leads to the development of hypertensive heart disease and congestive heart failure, aggravates and accelerates the course of atherosclerosis and exerts other well known deleterious effects. The role of humoral factors and vasoactive hormones is probably secondary. Hypertension increases the susceptibility of small and large arteries to atherosclerosis and leads to occlusive disease of the coronary and cerebral vessels, leading to myocardial infarction and stroke. Disease of the arterial media, beginning in childhood with deposition of calcium, is an important cause of arterial hypertension. Proper and prompt treatment of patients with hypertension can control symptoms and prevent its complications.

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STANLEY ULICK

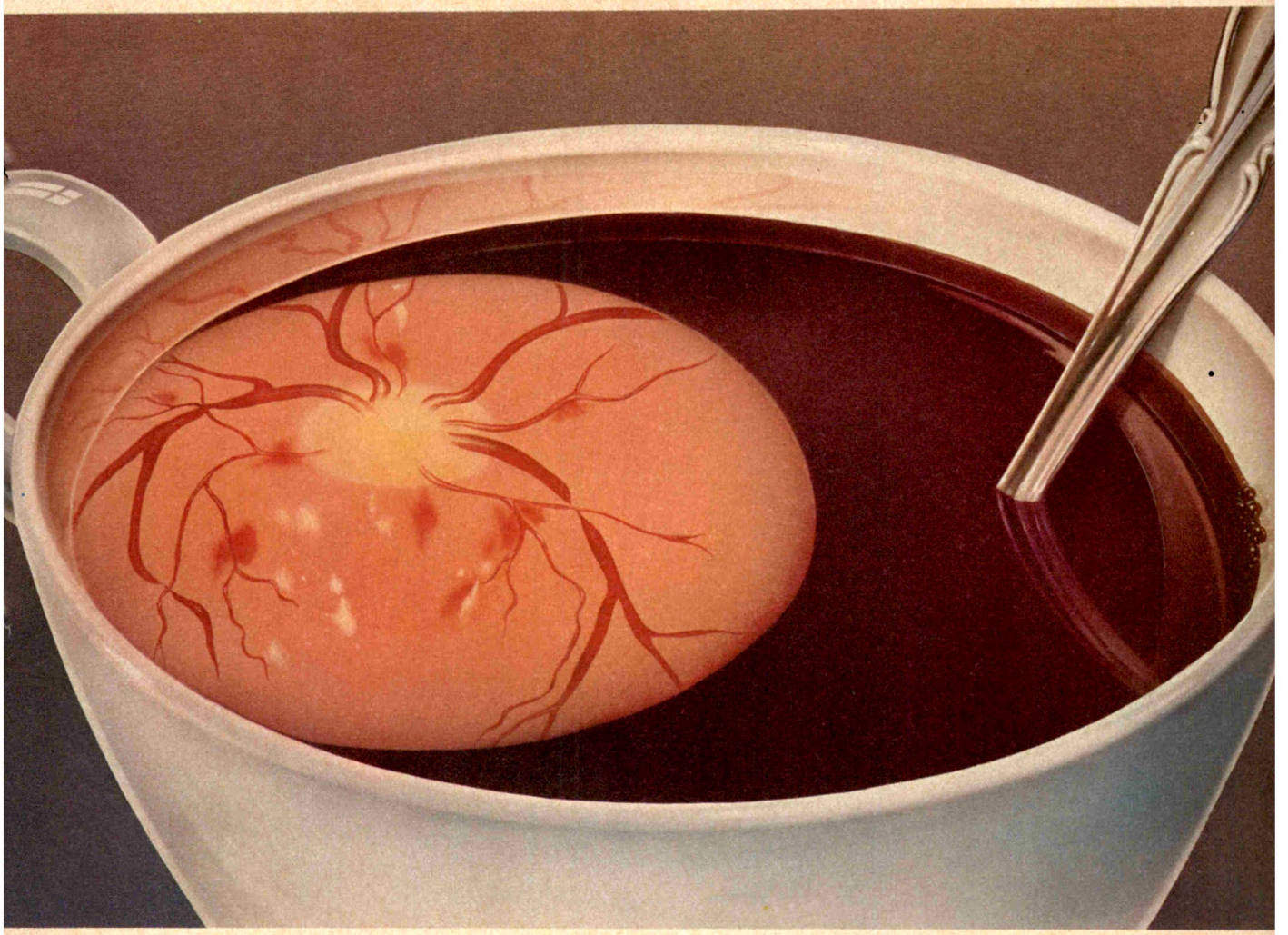
Neither significantly increased in experimental hypertension nor responsible for any appreciable effect in unselected patients with low renin essential hypertension, 18-hydroxy-11 deoxycorticosterone is increased in primary aldosteronism. It may indicate a histologic variant of the aldosteronoma, and appears to be an obligatory consequence of the secretion of fasciculata zone corticosterone since both the 11β- and 18-hydroxylase enzymatic functions of the fasciculata zone are related and may involve the same enzyme protein and catalytic site.

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Clonidine proved effective in the treatment of hospitalized hypertensive patients, achieving a rapid reduction of blood pressure in subjects with high and normal renin levels by acute inhibition of renin-angiotensin pressor mechanisms, and a more gradual antihypertensive effect associated with reduced sympathetic activity regardless of renin status. Reduction of aldosterone secretion is a result of clonidine-induced inhibition of renin release, thereby preventing fluid retention which may maintain the hypertensive state. This critical antirenin action of clonidine occurred in all patients.

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CLINICAL STUDIES

Acute Oral Testing for Determining Antiarrhythmic Drug Efficacy

I. Quinidine

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Acute oral drug testing with quinidine was used in 18 patients with high grade ventricular arrhythmia. This method involves administering a single large dose of the antiarrhythmic agent, monitoring heart rhythm by means of programmed trendscription and determining blood drug levels at selected intervals. After quinidine was given in a dose of 0.6 g, 10 patients had a positive response, defined as a 50 percent or greater reduction in ventricular premature beats and abolition of repetitive ectopic beats. Drug action began a mean of 88 minutes after administration, and the mean peak blood quinidine level was 3.2 ± 0.5 (standard error) μg/ml. Four patients had a paradoxic increase in arrhythmia. In nine patients the response to acute drug testing was compared with the response to maintenance quinidine therapy with doses of 1.2 and 1.8 g/day. The presence of arrhythmia was assessed with 24 hour ambulatory monitoring and exercise stress testing. With both techniques, seven of nine patients showed results concordant with those of acute testing. Disparity in results of the two methods of drug administration was explained by the serum concentration of quinidine. Acute oral drug testing provides a new approach for determining expeditiously whether quinidine is effective or hazardous in an individual patient.

Prevention of recurring ventricular arrhythmias and ventricular fibrillation largely depends on the use of drugs.[1] At present, there is no rapid method for determining the efficacy and appropriate dose of an antiarrhythmic agent for suppressing ventricular ectopic activity. Neither the particular ventricular rhythm disorder nor the type and extent of underlying heart disease aid in selecting a specific drug. When an antiarrhythmic agent fails to prevent recurrence, there is no certainty whether it is the proper drug or if the correct dose has been administered. There are additional difficulties in choosing an effective antiarrhythmic agent. If the arrhythmia does not provoke symptoms, repeated and costly Holter ambulatory monitoring sessions are required to determine whether a drug is of value. When the arrhythmia is sporadic and infrequent, there is no certainty, even with longer periods of monitoring,

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whether the drug being administered is effective. The problem becomes even more challenging when the patient is afflicted with life-threatening rhythm disorders, for then there is no permissible error in drug prescription..

We have developed a new method that enables rapid assessment of the effectiveness of a drug against ventricular arrhythmias. The method consists of acute drug testing and involves the following elements:

1. Administration of a single large oral dose of the selected drug.
2. Use of programmed trendscription to display the time course of drug action.[2]
3. Sampling of blood for drug concentration during this period of observation to permit correlations with onset and dissipation of antiarrhythmic or toxic effects.

This report describes the use of this approach for assessing the action of quinidine in controlling advanced grades of ventricular ectopic arrhythmias. The efficacy of this method was determined by comparing the effects of acute drug testing with the results of maintenance quinidine therapy. The maintenance program was of brief duration, and drug action was judged by means of exercise stress testing and 24 hour ambulatory electrocardiographic monitoring.

Materials and Methods

Subjects: The study population consisted of 18 patients referred to the Antiarrhythmic Clinic at the Cardiovascular Laboratory of the Harvard School of Public Health. Entrance into the study required a prevalence rate of ventricular premature beats exceeding 1/min during a 30 minute period of control monitoring. The following grading system for ventricular premature beats was employed[1,3]:

0	=	no ventricular premature beats
1	=	occasional, isolated (<30/hour)
1A	=	≤1/min
1B	=	≥2/min
2	=	frequent (>30/hour)
3	=	multiform
4	=	repetitive
4A	=	couplets
4B	=	salvos of three or more
5	=	early, with T wave interruption

All patients manifested high grades of ventricular ectopic activity. Seventeen of the 18 subjects had grade 4 arrhythmia. Of these, 13 had experienced ventricular tachycardia either as brief three to four beat paroxysms or as sustained disorders requiring cardioversion. Four had cardiac arrest due to ventricular fibrillation and, of these, three experienced ventricular fibrillation on more than one occasion.

There were 15 men and 3 women ranging in age from 26 to 81 years. Eleven of this group had coronary heart disease, 10 having experienced previous documented myocardial infarction. One patient had a hypoplastic left anterior descending coronary artery. Six patients, including five with recurrent ventricular tachycardia, had no demonstrable evidence of organic cardiovascular disease. One 26 year old man had an apical systolic click but was free of murmurs, cardiomegaly or echocardiographic evidence of mitral valve abnormality. Two of the six patients without evident structural heart disease had cardiac catheterization. Their coronary arteries were normal, and they had no observable hemodynamic or ventricular contraction disorders. Each patient had given informed consent for participating in this investigation.

Programmed trendscription: This method has previously been described.[2] The system consists of three components: a trendscriber, a programmer and a telemetery unit. Monitoring information is inscribed upon a circular drum. A heated stylus spirals downward at a speed of 6.25 mm/sec, that is, at one quarter the usual speed of the electrocardiographic recorder. Each line inscribes 1 minute of information and 30 lines can be written on a single page. The programming apparatus is a standard electronic clock that permits sampling at selected intervals ranging from 1 to 60 minutes. The telemetry transmitter is attached to the patient by means of two leads, one located at the right infrascapular area and one in the V_5 position, with one lead serving as a transmitting antenna.

Acute antiarrhythmic drug testing: Each patient was instructed to take no antiarrhythmic drugs for 48 hours. Breakfast was limited to tea and toast 2 hours before the test. Thirty minutes of control trendscription was carried out. A complete electrocardiogram was also recorded. Once the prevalence of ventricular premature beats was documented, the trendscription programmer was switched from a continuous to a sampling mode of 1 minute during every 3 minutes. This sampling rate permits ready recognition of trends in arrhythmia prevalence without undue loss of data. It also facilitates the ready visual scoring of frequency of ventricular premature beats. After the control period, each patient received 600 mg of quinidine sulfate by mouth. Subjects were seated in a comfortable reclining chair during the test. Reading material was provided, and the patients were encouraged to move about the room to relieve boredom during the long procedure. Quinidine blood levels were obtained hourly. At the time of blood sampling, lead V_3 or V_4 was recorded at 50 mm/sec for determining duration of the Q-T interval and width of the QRS complex. The test lasted for 5 hours. The objective was to record peak drug action and dissipation of its effect as well as the possible recurrence of arrhythmia. If no antiarrhythmic action was recorded by 3 hours after drug ingestion, the test was terminated. When arrhythmia was absent during control trendscription, exercise on a bicycle ergometer was employed hourly to precipitate arrhythmia and thereby help define drug action. This procedure was required in two patients, both of whom had previously experienced ventricular fibrillation.

Antiarrhythmic maintenance therapy: After completion of the acute drug testing, 10 of the 18 patients began maintenance therapy with oral antiarrhythmic doses of quinidine. Five of the 10 patients had had a positive response to acute oral testing, whereas 5 had not. The maintenance dose was 0.3 g every 6 hours or 1.2 g/day for 3 days. If ventricular arrhythmias were not suppressed but the patient had no untoward effects and was willing to participate, the dose was increased to 0.6 g three times during waking hours for a total of 1.8 g daily. After 48 hours the effect of the drug was determined with exercise testing and the result compared with results of the control exercise test performed before initiation of maintenance therapy. At the time of the exercise test, the blood quinidine level was measured. During the ensuing 24 hours ambulatory monitoring was carried out and upon return of the portable recorder, the blood quinidine level was again determined. Quinidine was assayed by the method of Edgar and Sokolow[4] which recovers 100 ± 5 percent (mean ± standard error) of quinidine at concentrations greater than 2 μg/ml. The means of the group data were compared using Student's t test, and, chi square testing was employed when appropriate.

Exercise stress testing: Patients exercised before and 48 hours after institution of maintenance quinidine therapy. The exercise test for provoking arrhythmia has previously been described.[5,6] Exercise was performed on a motorized treadmill with use of a Bruce protocol.[7] Silver-silver chloride electrodes in either the V_4 or V_5 position were used for recording. In addition to oscilloscopic monitoring, the entire test was trendscribed, and thus no ectopic activity was missed. The exercise testing was preceded by a 3 minute control electrocardiogram obtained in the supine position, followed by 1 minute of hyperventilation, and then a 1 minute record while the subject was standing.

End points for exercise were disabling fatigue, dyspnea, intensifying angina pectoris with continued effort, or major ventricular arrhythmia.[6] In the absence of these changes, the patient was encouraged to continue. S-T segment depression, emergence of multiform ventricular premature beats, couplets or three beat ventricular tachycardia did not constitute a reason for terminating a test. After completion of exercise, the patient assumed a supine position and was monitored for 10 minutes.

The exercise capacity, reasons for stopping the test, S-T segment changes and all arrhythmias were noted. The number and grade of ventricular premature beats in each minute of the control, exercise and postexercise periods were recorded. All tests were supervised by an experienced cardiologist. The exercise laboratory was fully equipped to respond to cardiac emergencies, but none were encountered in the course of this study.

Ambulatory monitoring: The method of 24 hour continuous electrocardiographic monitoring has previously been described.[1,8,9] A portable cassette tape unit was used. Patients were coupled to the monitoring apparatus with standard disposable silver-silver chloride electrodes placed in a modified lead II configuration. The compact recorder was attached to a belt worn around the waist and did not interfere with normal activity or even vigorous exercise. Patients were instructed to proceed with routine tasks and not to avoid their usual daily stresses.

Analysis of the 24 hour electrocardiographic record was accomplished with a three stage system of data processing.[3] The first involved the usual Holter screen of the 24 hour cassette at 60× real time. The second stage consisted of a semiautomated analysis, and the third constituted a quality control check. This last stage involved printout of a random hour of the 24 hour session in its entirety in a condensed form on a special XY plotter and was examined for each of the 60 minutes for prevalence and type of ventricular premature beats.

Results

Acute Quinidine Action

Of the 18 patients given 0.6 g of quinidine in a single oral dose, 10 showed an antiarrhythmic response. This was defined as a 50 percent or greater reduction in incidence of ventricular premature beats and complete abolition of grade 4 ectopic beats during a 30 minute period within 1 to 3 hours after administration of the drug as compared with conditions in the control period of similar duration. Two patients who were free of ventricular premature beats during the control trendscription had experienced ventricular fibrillation in the immediate past. In these two, bicycle exercise was required to provoke ectopic activity. The arrhythmia was suppressed during peak quinidine action when these patients underwent exercise. Among the 10 responders the frequency and severity of ventricular premature beats was less than among the 8 nonresponders (Table I). Thus, there was only 0.8 episode of ventricular tachycardia in the 30 minute control period among the 10 responders compared with 15.3 such episodes among the 8 nonresponders ($P < 0.001$). Among the responders, ventricular premature beats decreased from a mean of 10.6 to 1.3/min (88 percent reduction); among nonresponders there was a slight increase at the time of peak drug action compared with the control period (from 14.6 to 15.6/min).

TABLE I

Comparison of Quinidine Responders and Nonresponders During Acute Drug Testing

	Responders	Nonresponders
Total subjects (no.)	10	8
Subjects with heart disease (no.)	9	3
VPBs (mean frequency/min)	10.6	14.6
Grade 4A*	12.9	35.3
Grade 4B*	0.8	15.3
Quinidine blood level (μg/ml)		
Mean ± SE	3.2 ± 0.50	3.3 ± 0.53
Range	1.1 to 5.7	1.1 to 6.3

* Per patient during 30 minutes of control monitoring.
SE = standard error; VPBs = ventricular premature beats.

All but 1 of the 10 responders had heart disease, whereas 5 of the 8 nonresponders had no evidence of organic cardiovascular disease. One nonresponder with coronary heart disease had a 99 percent reduction in frequency of ventricular premature beats, but 4A arrhythmia was not suppressed. In another nonresponder with heart disease, the prevalence of ventricular premature beats remained unaltered (926 such beats during 30 minutes of the control period and 951 during 30 minutes after administration of quinidine), but 50 couplets and 42 beats of ventricular tachycardia were abolished after quinidine.

Onset of quinidine action in the 10 responders, defined as a 25 percent reduction in incidence of ventricular premature beats, occurred in a mean time of 88 minutes (range 30 to 150 minutes) (Fig. 1). In one patient a decrease noted immediately after ingestion of quinidine was probably related to a placebo effect.

Duration of drug action could be defined in four patients and ranged from 30 to 240 minutes. In the other six the duration exceeded the five hours of the test procedure. The mean drug level was 3.2 μg/ml ± 0.50 (standard error) in the 10 responders and 3.3 μg/ml ± 0.53 in the 8 nonresponders. The drug level ranged from 1.1 to 5.7 μg/ml in the former and from 1.1 to 6.3 μg/ml in the latter group. In four patients the mean drug concentration was 2.8 μg/ml at the time of recurrence of arrhythmia compared with a concentration of 3.8 μg/ml at the time of maximal ventricular premature beat suppression. The mean peak drug concentration for patients manifesting a more prolonged quinidine effect was not significantly different from that of the four patients with a briefer drug action.

Adverse reactions were not observed. However, in four of the eight nonresponders the arrhythmia was aggravated after administration of quinidine. The mean quinidine blood level in these four patients was 3.2 μg/ml, a value not statistically different from that of the responders. In three of the four patients, the increase in ventricular premature beats was associated with more frequent paroxysms of ventricular tachycardia (Fig. 2). In two patients grade 4A arrhythmia first increased while the quinidine blood level was rising and then was completely abolished (Fig. 3). Changes in heart rate, QRS width, P-R and Q-T interval durations are shown in Table II. Only the lengthening in Q-T interval after administration of quinidine achieved statistical significance. The mean increase was 49 msec.

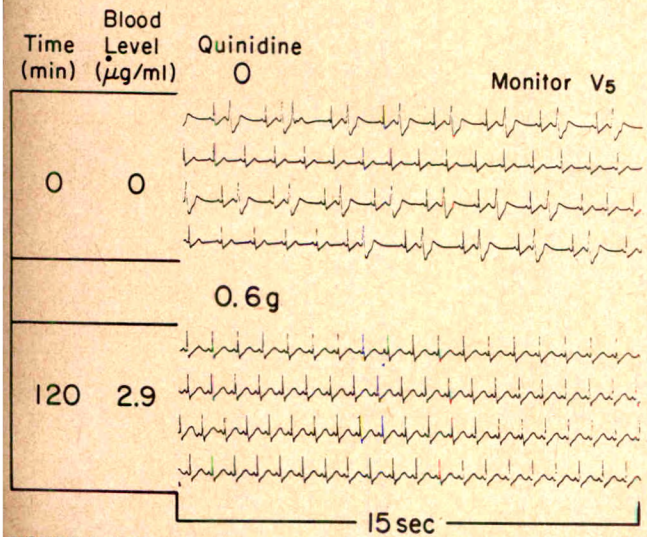


FIGURE 1. A 53 year old woman without organic heart disease but with grade 4A ventricular arrhythmia. During 30 minute trendscription she exhibited 665 ventricular premature beats. Within 90 minutes after oral administration 0.6 g of quinidine, the blood level was 2.9 μg/ml and all ventricular premature beats were abolished.

Comparison of Acute Drug Testing and Maintenance Therapy

Exercise: This comparison was conducted among nine patients, four with coronary heart disease, one with a hypoplastic left anterior descending coronary artery and four with no cardiovascular disease. Two exercise tests were carried out 48 hours apart, the first while the patient was without drug and the second while he was receiving quinidine. The level of exercise was the same during both tests, as judged by duration of exercise and increase in heart rate. The duration of exercise was 7.8 minutes and the increase in heart rate was 72 beats/min before administration of quinidine compared with 7.6 minutes and 74 beats/min, respectively, after administration of quinidine. Five of the nine patients had two

TABLE II

Electrocardiographic Changes After Oral Administration of 0.6 g of Quinidine Sulfate as a Single Dose

	Control	After Quinidine
Heart rate (beats/min)	71 ± 11.07	72 ± 12.42
P-R (sec)	0.18 ± 0.036	0.17 ± 0.028
QRS (sec)	0.085 ± 0.0075	0.09 ± 0.015
Q-T (sec)	0.38 ± 0.05	0.416 ± 0.06*

Values expressed as mean ± standard error.
* $P < 0.001$.

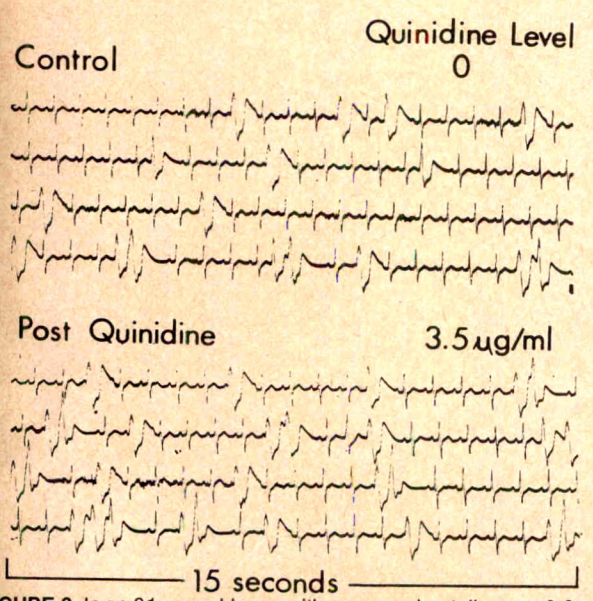


FIGURE 2. In an 81 year old man with coronary heat disease, 0.6 g of quinidine was without effect on the frequency of ventricular premature beats; however, grade 4B arrhythmia increased. The three beat ventricular tachycardia evident in the bottom strip was not observed during the control period.

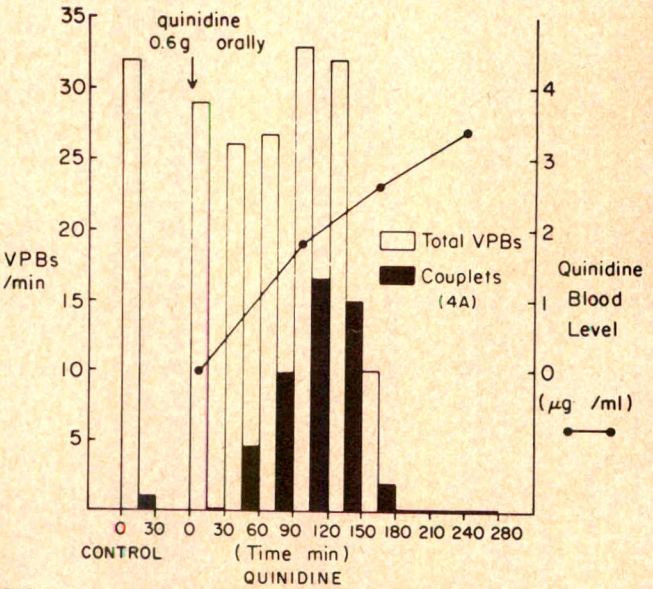


FIGURE 3. In a 69 year old man with subtherapeutic blood levels of quinidine there was a striking increase in couplets (4A arrhythmia) from a rate of 1/min in the control period to 15/min when the quinidine concentration was 1.8 μg/ml. When the blood level reached 3.4 μg/ml, all ventricular premature beats (VPBs) were abolished.

successive 3 day courses of 1.2 and 1.8 g/day of quinidine.

Of this group of nine patients, four had and five had not responded to acute drug testing. When the results of acute drug testing were compared with results of exercise exposure of arrhythmia during maintenance therapy, seven patients had a concordant response and two a discordant response. All four patients who responded to acute drug testing also showed suppression of arrhythmia with exercise. Among the five who failed to respond during acute drug testing, three had a similar response with exercise and two a discordant response (Table III). In one nonresponder during acute drug testing, the quinidine blood level was only 1.1 μg/ml. With a similar blood level of 1.5 μg/ml during maintenance therapy of 1.2 g/day, the patient likewise failed to respond. However, when he was receiving 1.8 g/day, the blood level was 3.7 μg/ml and a substantial reduction in ventricular premature beats was observed. In the second nonresponder during acute drug testing, the quinidine level had been 2.6 μg/ml. However, with maintenance therapy of 1.2 g/day, the blood concentration was 4.1 μg/ml and ventricular premature beats were significantly reduced. When the dose was increased to 1.8 g, resulting in a blood level of 6.1 μg/ml, ventricular ectopic activity was abolished during exercise.

In two patients exercise-evoked arrhythmia was greater during maintenance therapy with 1.2 g/day of quinidine than during control testing (Fig. 4). Both patients were nonresponders during acute drug testing. In one, at a blood quinidine level of 1.5 μg/ml, ventricular premature beats increased by 60 percent, the incidence of couplets doubled and three paroxysms of ventricular tachycardia emerged that had not been present during the control exercise period.

Twenty-four hour monitoring: Monitoring was carried out during maintenance quinidine therapy in nine patients, four of whom had responded to acute drug testing. Concordance between the results of acute drug testing and maintenance therapy was observed in seven of the nine (Table IV). Four patients had suppression of arrhythmia while receiving maintenance therapy; one required 1.8 g/day for suppression. The five who did not respond had a more advanced grade of ventricular premature beats (Table V). This nonresponse was evident in patients with grades 3, 4A and 4B

TABLE III

Comparison of Acute Drug Testing and Quinidine Maintenance Therapy With Exposure of Arrhythmia by Means of Exercise in Nine Patients

	Maintenance Therapy (Exercise)		
Acute Drug Testing	Responders	Non-responders	Quinidine Blood Level (μg/ml)
Responders	4	0	3.8
Nonresponders	2	3	3.3
Quinidine blood level (μg/ml)	4.3	3.9	

TABLE IV

Comparison of Acute Drug Testing and Quinidine Maintenance Therapy With Exposure of Arrhythmia by Means of 24-hour Monitoring in Nine Patients

	Maintenance Therapy (Monitoring)		
Acute Drug Testing	Responders	Non-responders	Quinidine Blood Level* (μg/ml)
Responders	3	1	4.7
Nonresponders	1	4	3.3
Quinidine blood level* (μg/ml)	4.0	3.9	

* The differences in quinidine level are not significant.

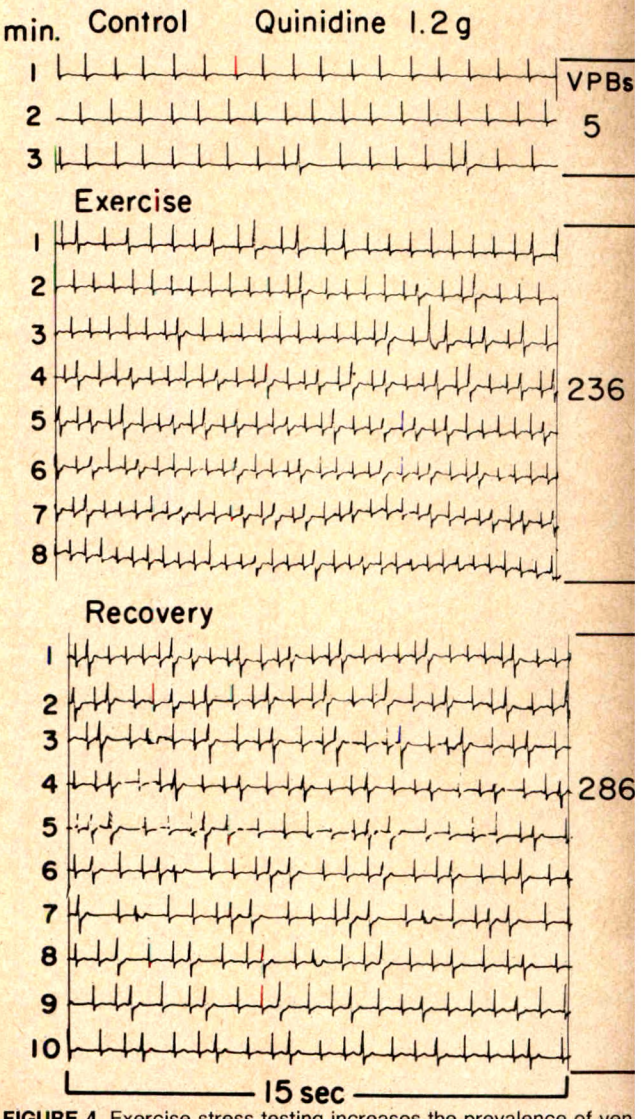


FIGURE 4. Exercise stress testing increases the prevalence of ventricular premature beats (VPBs) during treatment with 1.2 g/day of quinidine in a patient who failed to respond to acute drug testing.

TABLE V

Distribution of Hours of Grades of Ventricular Premature Beats Among Nine Patients Receiving Maintenance Quinidine Therapy

	no.	Quinidine Blood Level μg/ml	Control Period							During Quinidine Maintenance Therapy						
			0	1A	1B	2	3	4A	4B	0	1A	1B	2	3	4A	4B
Responders	4	4.1*	1	2	2	19	7	9	2	6	7	6	3	3	0	0
Nonresponders	5	4.4*	2	0	0	18	13	12	10	2	0	0	20	15	7	1

* Five patients (four nonresponders and one responder) received 1.8 g/day of quinidine; the other four received only 1.2 g/day.

arrhythmia and was most striking in those with grade 4B arrhythmia. Ventricular tachycardia was evident in 2 of the 24 hours of monitoring in the responder group compared with 10 hours among the nonresponders. A higher quinidine level was encountered among the five nonresponders because four of the five were receiving the higher maintenance dose of 1.8 g/day. Although the nonresponders as a group had no reduction in frequency of ventricular premature beats, they had a substantial reduction in advanced grades 4A and 4B.

The discordant response observed in two patients (Table V) may be explicable on the basis of the quinidine levels obtained during the two tests. Thus in one nonresponder, a peak blood level of 2.3 μg/ml was obtained with acute testing. During maintenance therapy (1.2 g/day) with a blood concentration of 3.9 μg/ml, grade 2 arrhythmia was reduced from 19 hours during the control period to 3 hours, and all advanced grades of arrhythmia were abolished. The opposite findings were noted in the second patient with a discordant response. During acute testing, when a peak quinidine blood level of 5.7 μg/ml was noted, ventricular premature beats were abolished. During maintenance therapy with 1.2 and 1.8 g/day, the respective blood levels were 1.1 and 3.1 μg/ml, and no suppression of arrhythmia was observed.

Discussion

The selection of an effective antiarrhythmic regimen relates to the choice of a suitable drug, determination of an appropriate dose schedule and establishment of an adequate therapeutic end point. Ideally, testing for an antiarrhythmic agent should consist of a double-blind crossover design protocol. There should be two or more control sessions for establishing reproducibility of procedures, followed by administration of placebo and one or more sessions with several doses of the drug being tested ending with a placebo phase. During each of these sessions, exercise stress testing and 24 hour ambulatory monitoring should be carried out to ascertain drug action. Such a study is rarely possible to implement because of cost and poor patient adherence. Furthermore, if several drugs fail, months may be required to establish an effective drug program. Yet once an effective antiarrhythmic drug is identified, there is no assurance that it can be safely used over prolonged periods. Thus the much expanded effort may be an exercise in futility. This type of design may also be hazardous for the patient. If the patient has a potentially malignant arrhythmia, such prolonged intervals without adequate protection cannot be sanctioned.

It may be argued that in the presence of life-threatening rhythm disorders a prophylactic antiarrhythmic program should be worked out while the patient is hospitalized. However, the hospital is a poor environment for judging drug efficacy against sporadic arrhythmias whose recurrence may depend on psychologic stresses encountered only at home or at work. The hazard to patients may also derive from the antiarrhythmic drug, especially those with quinidine-like properties. The greatest danger is the unheralded syncope due to ventricular fibrillation that occurs 1 to 3 hours after administration of the last dose.[10–13] In our study, 4 of the 18 patients had increased frequency of ventricular premature beats and 3 patients had more paroxysms of ventricular tachycardia. These rebound reactions were noted when the serum level was in a low therapeutic range of 1.0 to 2.0 μg/ml. Such levels are likely on a maintenance program when the patient delays or forgets entirely to take a dose. It thus appears that present methods for selecting an effective suppressive drug for major recurring ventricular arrhythmias are inappropriate and unwieldy.

Acute drug testing: A new method has been developed that obviates some of these limitations.[2,14] The method of acute drug testing consists of three elements: administration of a large single oral dose of the antiarrhythmic agent, careful and continuous monitoring of drug effect, and measurement of blood drug levels at times when heart rhythm is altered or toxic effects are in evidence. We selected 0.6 g of quinidine as the test dose to be taken orally. This represents half the usual daily maintenance dose of 1.2 g, which generally provides a level of 2.5 to 3.5 μg/ml, within the considered therapeutic range.[15–17] It was presumed that such a single large oral dose would rapidly result in a therapeutic blood level. Indeed, this was the case; among the 10 responders the mean quinidine concentration achieved at the time of peak drug action was 3.2 μg/ml.

Potential hazards of method: A significant question relates to the potential hazard of administering a single large dose of quinidine. No serious untoward reactions were encountered in any of our 18 patients. Because only one dose of the drug is given it is unlikely that serious toxicity other than aggravation of arrhythmia or

some idiosyncratic reaction will occur. The attendance of a physician and the continuous monitoring of heart rhythm provide greater safety than is provided in the usual procedure of prescribing a drug to be taken without close medical surveillance. The only changes noted were those in Q-T interval, which had a mean prolongation of 49 msec. Lengthening in QRS duration has been reported as a consistent finding after administration of quinidine, but the increase is only about 10 percent and requires special instrumentation for detection.[18]

Programmed trendscription: Continuous monitoring of heart rhythm during acute drug testing was accomplished with trendscription.[2,14] Current monitoring methods, providing on-line rhythm information involving oscilloscopic displays or tape printout, do not permit ready recognition of trend in changes of sporadically recurring arrhythmias. When a single lead is printed out continuously the surfeit of output, aside from cost, soon ensnarls one in reams of paper and defeats human capacity for analysis. Trendscription presents on-line hard copy of a compressed record that permits prompt recognition of patterns of arrhythmia. When this method is coupled with appropriate programming, trends of ectopic activity can be easily appreciated, thus enabling blood sampling at precise stages of antiarrhythmic drug action. The continuous availability of rhythm data is indispensable for assuring patient safety during acute drug testing.

Quinidine blood levels and antiarrhythmic effect: Acute drug testing has as its central hypothesis that the key factor in antiarrhythmic drug action is a critical blood concentration distinctive for each patient. During acute quinidine administration the mean blood level for the 18 patients was 3.25 ± 0.53 (standard error). In only three patients was the blood level less than 2.0 μg/ml, and in two of these with levels of 1.1 and 1.2 μg/ml, respectively, effective suppression was demonstrated. The patient having the lowest blood quinidine level after acute administration had 229 ventricular premature beats, 34 couplets and 5 paroxysms of ventricular tachycardia during the control 30 minute trendscription. After acute administration of quinidine, although the peak blood level was only 1.1 μg/ml, the total count of ventricular premature beats was reduced to 2 and there were no advanced grades of arrhythmia during a similar 30 minute period of trendscription. At the other extreme, the highest blood level achieved was 6.3 μg/ml, and the patient with this level failed to show a positive drug effect; 70 ventricular premature beats observed during the control period trendscription were increased to 109 at the time of the highest drug concentration. Furthermore, there was no difference in drug concentration between those responding and those failing to suppress arrhythmia during acute drug testing. These observations indicate that the aim of therapy with quinidine should not be a particular blood drug level since a therapeutic response is highly individual and depends on factors in addition to the specific concentration reached.

Acute drug testing as predictor of success of maintenance therapy: In seven of nine patients, the response to acute drug testing predicted the result with maintenance therapy when exposure of arrhythmia was achieved by either maximal exercise stress testing or 24-hour monitoring. The two failures were related to disparities in blood level achieved by the two methods. If during acute testing no response is observed and the blood level is well above the expected therapeutic range it is unlikely that maintenance therapy will prove effective. The converse may also be true; that is, if acute drug testing suppresses the ventricular arrhythmia, it is highly likely that maintenance therapy will also suppress it provided that equivalent blood levels are achieved.

Clinical implications: Acute drug testing with quinidine thus has significant concordance with more accepted methods for assessing drug efficacy. Such testing, when carefully interpreted with assessment of the duration and magnitude of arrhythmia suppression, the occurrence of rebound and the peak drug level reached, permits a sound estimate of the effect of maintenance therapy with quinidine. Whether this approach is applicable to other antiarrhythmic agents remains to be demonstrated. Preliminary studies have yielded similar results with procainamide. If the action of a drug depends on a slowly developing myocardial concentration, this method will probably prove unsuitable. At present, this approach commends itself, especially for the patient who has been successfully resuscitated from ventricular fibrillation and exhibits a profusion of ventricular arrhythmia. In such patients there is an urgency to define an effective antiarrhythmic program and provide a "fail safe" system wherein more than one drug is used.[14]

The administration of antiarrhythmic drugs, especially in larger doses, exposes the cardiac patient to the potential hazard of serious arrhythmias. Indeed, 4 of our 18 patients exhibited aggravation of ectopic activity after administration of quinidine. Since acute drug testing to date has been tried in relatively few subjects, the procedure should be deemed experimental. It must be carried out under a tight protocol with close medical supervision.

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Undesirable Cardiac Arrhythmias Associated With Rate Hysteresis Pacemakers

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The introduction of the ventricular inhibited pulse generator with the feature of rate hysteresis has been associated with a variety of rhythm disturbances, some causing serious concern. This pulse generator has two different pacing rates: (1) the automatic rate, which is the interval between two successive paced beats (usually 860 msec or 70/min), and (2) the hysteresis interval, which results in a 1,000 msec delay between a sensed cardiac contraction and the next pacemaker discharge. The hysteresis interval after a sensed signal may result in long pauses that may predispose to the development of serious cardiac arrhythmias. Two examples of this type of complication were recently observed. One patient had bigeminal rhythm with mechanically ineffective cardiac contractions and an effective cardiac rate of 35/min; he experienced dyspnea and weakness during these prolonged episodes. Another patient had repeated episodes of ventricular fibrillation. The cardiac arrhythmias were not controlled by antiarrhythmic agents, and both patients required replacement of the pulse generator.

The proposed advantages of pulse generator hysteresis are (1) prolongation of battery life, and (2) maintenance of effective atrial transport; these advantages may be outweighed by undesirable cardiac arrhythmias that may be associated with this mode of pacemaker function. Rate hysteresis cardiac pacemakers should be reserved for patients having predominantly sinus rhythm without ventricular irritability. In patients with frequent ectopic ventricular activity, atrial fibrillation or high degree atrioventricular block, the rate hysteresis pacemaker offers no advantage over the conventional demand pacemaker. For patients with frequent ectopic ventricular activity not easily controlled by antiarrhythmic agents, consideration should be given to the use of a permanent demand pacemaker with external rate control, which may provide greater flexibility in arrhythmia management.

Permanent cardiac pacemakers have been available for approximately 15 years. With improvements in design and reliability of component electronic parts, the demand cardiac pacemaker has emerged as the type most frequently utilized. One variant of the demand cardiac pacemaker, produced by several manufacturers,* has a rate hysteresis mode of operation. This type of pacemaker has two different pacing rates: (1) the automatic rate, and (2) the hysteresis interval, which results in a 1,000 msec delay between a sensed signal and the next pacemaker discharge. As with all cardiac pacemakers, the rate hysteresis pacemaker is associated with arrhythmias peculiar to its mode of operation. Because the hysteresis interval may result in long pauses in the cardiac cycle, these arrhythmias may be serious.[1,2] This paper reports two examples of this type of complication.

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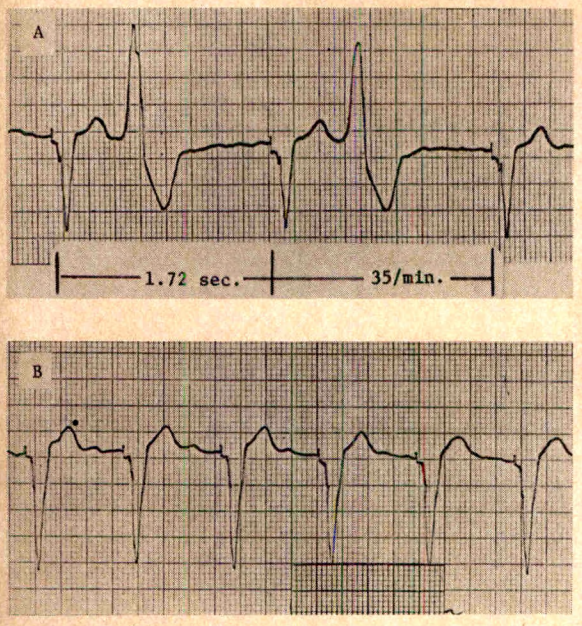


FIGURE 1. Case 1. Rhythm strips. **A,** during bigeminal rhythm. Because the premature ventricular contractions were mechanically ineffective, the effective cardiac rate was 35 beats/min. There was a 1.72 second pause between effective cardiac contractions. **B,** after replacement of the original pulse generator with one set at a rate of 80/min. Ectopic ventricular activity was generally abolished. When a premature ventricular contraction did occur, the pause between effective cardiac cycles was 1.4 seconds.

Case Reports

Case 1

A 77 year old man had a Medtronic model 5943 pacemaker, with an automatic rate of 70/min and the feature of rate hysteresis, implanted because of intermittent third degree heart block and associated bifascicular block. In addition, he had compensated congestive heart failure and cardiomegaly. Approximately 1 year later, he was noted to have bigeminal rhythm with an effective peripheral pulse rate of 35/min because the mechanically ineffective premature ventricular contractions failed to produce a peripheral pulse (Fig. 1A). During the episodes of bigeminal rhythm, which persisted for up to several days, the patient experienced fatigue, weakness and shortness of breath. Administration of quinidine sulfate in an attempt to decrease ectopic ventricular activity resulted in an episode of ventricular fibrillation. Subsequent treatment with procainamide, in doses up to 3 g/day, had little success in suppressing the ventricular bigeminy.

For this reason the patient's pulse generator was replaced with a Medtronic model 5963 pacemaker set at an automatic rate of 80/min. The frequency of the ectopic ventricular activity was thus reduced as a result of the faster automatic rate and the shorter pause after a sensed beat (Fig. 1B) and the effective peripheral pulse rate was increased even in the presence of ectopic contractions. The replacement pulse generator selected for this patient was chosen because the model allows one to set the optimal pacing rate for the patient and permits noninvasive alteration of this rate as the patient's needs change. The patient's symptoms decreased during the next 4 months. His subsequent death was attributed to intractable congestive heart failure.

Case 2

A 79 year old man had a Medtronic model 5943 pacemaker, with an automatic rate of 70/min and the feature of rate hysteresis, implanted because of second and third degree heart block. Eight months after implantation, frequent ectopic ventricular activity was noted. An attempt to suppress this ventricular arrhythmia with procainamide was associated with a lupus-like reaction. Subsequently, quinidine sulfate therapy was started for the control of the ventricular premature contractions. The patient remained asymptomatic for 8 months when, 2 weeks before readmission to the hospital, he began to experience periods of light-headedness.

On admission, the patient had several syncopal episodes. In the emergency room, he had frequent premature ventricular contractions and an episode of ventricular fibrillation that required electrical defibrillation (Fig. 2). There was no evidence of pacemaker malfunction. An attempt to control the ventricular irritability with increased doses of quinidine was apparently successful for several days. Then frequent episodes of ventricular fibrillation developed that required repeated electrical defibrillation. At that time, the pulse generator demonstrated intermittent failure to capture. The patient's clinical course was ultimately stabilized with insertion of a temporary transvenous pacemaker and continuation of the quinidine therapy. A Medtronic model 5950 pacemaker set at an automatic rate of 72/min was chosen as a replacement unit for this patient because it did not have the feature of rate hysteresis. The patient has been receiving maintenance treatment with quinidine since that time and has had a stable cardiac rhythm with no syncopal episodes.

Discussion

Demand pacemakers with a rate hysteresis feature have two different pacing intervals: (1) the automatic rate, which is the interval between two successive paced beats (usually 860 msec or 70 beats/min), and (2) the hysteresis interval, which results in a delay of usually 1,000 msec between a sensed cardiac contraction and the next pacemaker discharge. The proper function of a rate hysteresis pacemaker is shown in Figure 3. As a result of the longer hysteresis interval, there may be pauses of up to 2 seconds, which may predispose to the development of serious cardiac arrhythmias.

Advantages of rate hysteresis pacemaker: Pacemakers with the rate hysteresis feature have been reported to have several theoretical advantages. First, in patients with intermittent atrioventricular (A-V) block, battery life may be prolonged since only the sensing circuit, which requires less current, is operative when the intrinsic cardiac rate is higher than 60 beats/min. Second, atrial transport function is maintained during sinus rhythm at rates above 60 beats/min. These potential advantages are limited, however, to patients with sinus rhythm and a heart rate of 60 to 70 beats/min. When the intrinsic rate exceeds 70 beats/min, all demand pacemakers with an automatic rate of 70/min utilize only the sensing circuit and allow maintenance of effective atrial transport if sinus rhythm is present. Thus, Friedberg and Barold[2] doubt that the rate hysteresis feature results in significant prolongation of battery life and question whether the maintenance of effective atrial transport makes a physiologically important contribution to cardiovascular function in the

vast majority of patients within this narrow range of heart rates.

Disadvantages and complications of rate hysteresis pacemaker: The potential advantages of a pacemaker with the rate hysteresis feature must be weighed against the disadvantages of this system. As a result of the mode of operation of this type of puls generator, a patient having a pacemaker with an aut matic pacing rate of 70/min may experience paradoxic slowing of the cardiac rate to 60 to 70/min when sinu rhythm or an ectopic focus is present with a rate of 6 to 70/min (Fig. 3).[3] Such a clinical finding may be co

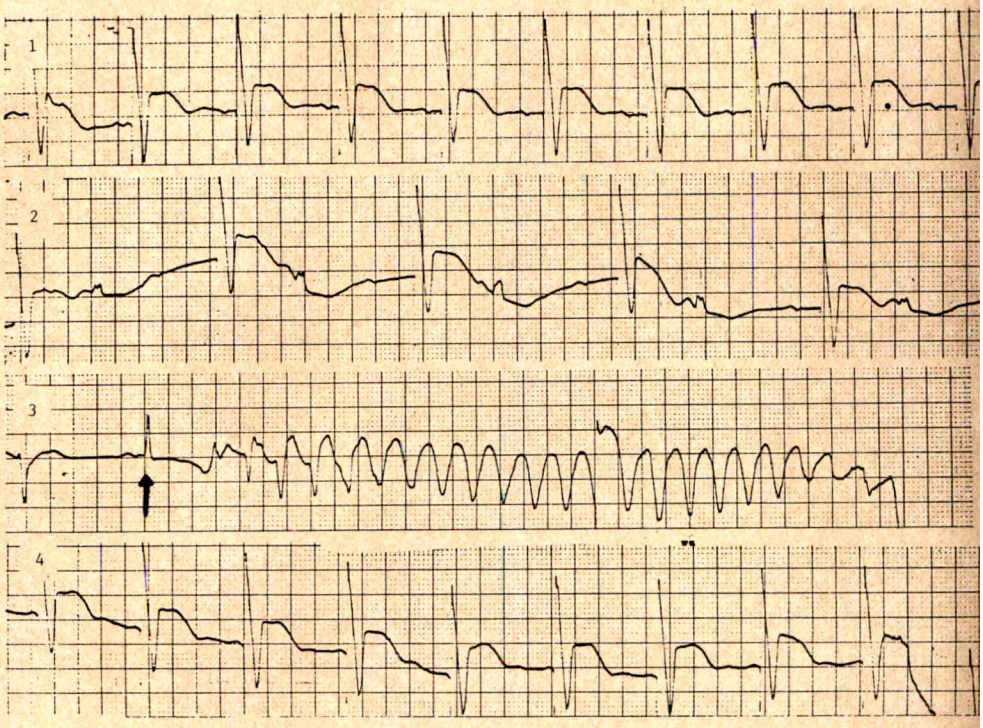


FIGURE 2. Case 2. Continuous rhythm strip showing the events preceding an episode of ventricular fibrillation that resulted in syncope and required electrical defibrillation. The **top panel** reveals a normally functioning demand rate hysteresis pacemaker discharging at an automatic rate of 70/min. The **second panel** shows the development of a bigeminal rhythm with an effective cardiac rate of 35/min. The first QRS complex in the **third panel** is a junctional escape beat. The next complex (**arrow**) is initiated from a sinus focus with a P-R interval of 0.20 second and a prolonged Q-T interval of approximately 0.56 second. A premature ventricular contraction falling in the vulnerable period of repolarization of the second QRS complex results in ventricular fibrillation. Electrical defibrillation (at the end of the **third panel**) restores the paced rhythm originally present in the **top panel.** The prolonged pauses (1,000 msec) associated with the bigeminal rhythm facilitated the development of the escape rhythm and the subsequent episode of ventricular fibrillation.

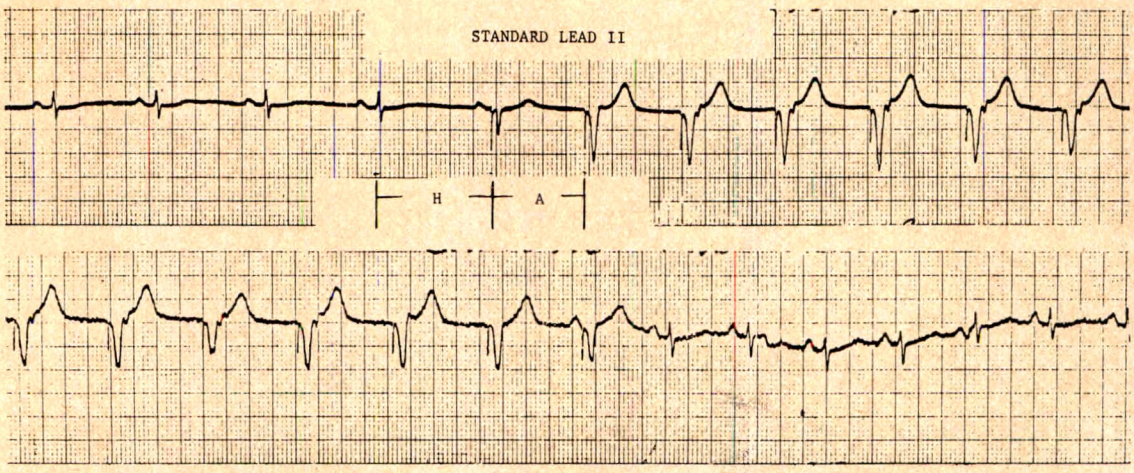


FIGURE 3. Rhythm strip from a properly functioning demand cardiac pacemaker with an automatic rate of 70/min and the feature of rate hysteres The first four complexes represent normal sinus rhythm at a rate of 60 to 70/min, which is sufficient to inhibit the cardiac pacemaker becau there is a 1,000 msec delay between the sensed QRS complex and the next pacemaker discharge (the hysteresis interval). The pacemaker do not discharge until the pause after the last sensed QRS complex exceeds 1,000 msec, as is the case between complexes 4 and 5 (designated for hysteresis interval). In this instance, the fifth complex represents a fusion beat. The next paced beats occur at the automatic pacemaker dischar rate of 70/min (designated A for automatic rate). The pacemaker rhythm is finally suppressed by the emergence of a sinus rhythm at a rate of a proximately 90/min. This rhythm strip illustrates the manner in which a patient with a rate hysteresis pacemaker may have paradoxical slowi of the heart rate below the automatic discharge rate of the pacemaker when an independent rhythm occurs with a rate between 60 and 70/mi

using and is often misinterpreted as pacemaker failure by those unfamiliar with this mode of pulse generator operation.

When the sensing circuit of the pacemaker is recycled by a mechanically ineffective extrasystole (Case 1, Fig. 1) or incorrectly by a physiologic or interfering electrical stimulus, there can be a prolonged period of asystole of up to 2 seconds. Such periods of asystole (1.4 seconds) have been reported after a sensed P wave superimposed on a T wave.[1] As in our Case 1, a mechanically ineffective systole results in periods of 1.72 seconds between effective cardiac contractions with a resultant cardiac rate of 35/min that represents a significant decrease from the automatic rate of 70/min. The hysteresis mode of pacemaker operation tended to perpetuate the bigeminal rhythm observed in our Case 1 through the rule of bigeminy.[4] Such an arrhythmia has been termed a frustrating bigeminy.[2]

The presence of frequent ventricular ectopic activity in our Case 2 (Fig. 2, panel 2) resulted in a slow cardiac rate and preceded the development of an episode of ventricular fibrillation with resultant syncope. The long pauses in the cardiac cycle predisposed to the development of ventricular irritability as a result of prolongation of the refractory period and increased nonuniformity of the refractory period.[5] These factors enhanced the likelihood of the development of ventricular fibrillation, which occurred in this patient (Fig. 2, panel 3) when a premature ventricular impulse fell in the vulnerable period of a preceding impulse having a prolonged Q-T interval.[6]

In both patients, the use of antiarrhythmic agents was ineffective in controlling the ventricular irritability and both patients had documented episodes of ventricular fibrillation while they were taking quinidine. Although the exact relation between the administration of quinidine and the subsequent development of ventricular fibrillation cannot be fully defined, the combination of the administration of quinidine and the prolonged pauses in the cardiac cycle as a result of the rate hysteresis feature of the cardiac pacemaker may have predisposed to the development of ventricular fibrillation in both of these patients.[7,8]

Indications for choice of pacemaker: Ultimately, both patients required replacement of the pulse generator for better control of cardiac rhythm. Accordingly, we recommend that due consideration be given to the mode of pacemaker operation in the initial choice of a pulse generator. Demand pacemakers with rate hysteresis should be reserved for patients who have a satisfactory underlying conducted sinus rhythm (60/min) without ventricular irritability and who only occasionally experience periods of bradycardia requiring cardiac pacing. These patients are most likely to benefit from the reported advantages of a rate hysteresis pulse generator. On the other hand, in patients with frequent ectopic ventricular activity, atrial fibrillation or high degree A-V block, the rate hysteresis pacemaker offers no advantage over the conventional demand pacemaker. Furthermore, some patients may experience undesirable cardiac arrhythmias as a result of the longer interval between the last sensed impulse and the next paced beat. The resulting cardiac arrhythmias may be of serious concern and outweigh any potential advantage provided by the rate hysteresis feature.

Although the hysteresis interval increases the likelihood of cardiac arrhythmias, arrhythmias similar to those associated with the rate hysteresis pacemaker may be seen with other types of cardiac pacemaker. Thus, in patients who require permanent cardiac pacing and who have recognized ectopic ventricular activity that is not easily controlled with standard antiarrhythmic agents, consideration should be given to implantation of a permanent demand pacemaker with an external rate adjustment feature. Such a pacemaker permits one to choose an appropriate pacing rate for overdrive suppression of the ectopic ventricular focus[9] and provides greater flexibility in the management of cardiac arrhythmias that may develop after pacemaker implantation.

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Propranolol-Induced Reduction of Signs of Ischemic Injury During Acute Myocardial Infarction

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The effect of intravenous administration of propranolol (3 to 10 mg) wa studied in 12 patients with acute anterior transmural myocardial infarctio within the first 8 hours from the onset of pain. Criteria for inclusion in th study were persistence of ischemic pain, S-T segment elevation of 0. or more mv in at least two standard precordial leads, heart rate of 80 c more beats/min, mean arterial pressure of 75 or more mm Hg and cardia index of 2.5 or more liters/min per m^2. Within 30 minutes of administratio of propranolol, the sum of S-T segment elevations from leads V_1 throug V_6 (ΣST_6) and the average S-T segment elevation over the left precordiu recorded from multiple unipolar leads ($\overline{ST}$) decreased significantly by 4 and 39 percent, respectively. At the same time, there was a significa reduction in heart rate (from 100 ± 3 [standard error of the mean] to 7 ± 4 beats/min), mean arterial pressure (from 112 ± 6 to 95 ± 5 mm Hg and cardiac output (from 6.1 ± 0.3 to 4.1 ± 0.3 liters/min). Pulmona capillary wedge pressure remained unaltered. Four hours later the he modynamic variables had returned to control level, but the beneficial effe on myocardial injury persisted. These electrocardiographic changes we accompanied by resolution of ischemic pain and cessation of ventricul arrhythmias. The effects of propranolol were more pronounced in patien with angiographically demonstrable flow to the affected area of myo cardium. Thus, administration of propranolol in the early hours of myo cardial infarction can significantly reduce the signs of myocardial ischem injury without excessively depressing myocardial function.

Several hours after the onset of the ischemic event the extent of my cardial damage in patients with acute myocardial infarction is delineate However, in the very first hours the injury to the myocardium is still a ongoing process, that is, it is in a reversible phase, and thus it is co ceivable that its course can be modified. This period of ongoing ischem during acute infarction is manifested by pain, S-T segment elevati and ventricular irritability, and its persistence indicates the continuati of the process of infarction.[1] Should the progression of ischemic inju be interrupted either spontaneously or therapeutically, these signs a symptoms of ischemia will subside. It is well recognized that treatme of myocardial ischemia as manifested by angina pectoris is effective wh the balance of myocardial oxygen supply and demand is favorably i fluenced either by an increase in oxygen supply, as in the case of corona artery bypass surgery, or by a reduction in oxygen requirement, as in t case of propranolol therapy.[2–4] Because acute myocardial infarcti represents one end of the spectrum of ischemic heart disease, it w suggested[5,6] that the same concepts of ameliorating the balance betwe oxygen requirement and delivery are applicable. Therefore, in this stu we examined the effect of beta adrenergic blockade on the signs ischemic injury in patients in the early hours after acute transmu anterior myocardial infarction.

From the Departments of Medicine of the Massachusetts General Hospital and Peter Bent Brigham Hospital, Harvard Medical School, Boston, Mass. This study was supported in part by U. S. Public Health Contract 1 P17HL17665-01 (SRC) (Ischemia SCOR), National Heart and Lung Institute Contract N01-HV-53000, National Institutes of Health, Bethesda, Md. and a grant from the John A. Hartford Foundation, New York, N. Y. Manuscript received March 29, 1976; revised manuscript received June 14, 1976, accepted June 16, 1976.

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Materials and Methods

Patients with myocardial infarction who were admitted to ıe coronary care unit of the Massachusetts General Hospital ere screened for entry into the study. They were selected only they satisfied all of the following criteria: (1) acute anterior ansmural myocardial infarction less than 8 hours after the nset of pain; (2) persistent ischemic pain incompletely reeved by the usual doses of opiates and nitroglycerin; (3) S-T gment elevation of 0.3 or more mv in at least two standard recordial leads; (4) absence of atrioventricular or intravenicular conduction abnormalities; and (5) absence of pulonary contraindications for propranolol.

Measurements: After giving informed consent, the paents were transferred to the intensive study area for instrumentation with a pulmonary arterial flow-directed catheter, radial arterial cannula and continuous polygraphic pressure and electrocardiographic monitoring. Cardiac output was measured by the thermal dilution method. Standard 12 lead electrocardiograms and multiple unipolar precordial leads were recorded serially. The magnitude of ischemic injury was estimated by the level of subjective pain rated by the patient on a scale of 0 to 10 and by the average S-T segment elevation of the precordial map ($\overline{ST}$) and the sum of S-T segment elevation of the six standard precordial leads (ΣST_6).

The sequence of measurements during the initial hour in the intensive study area was: first, 12 lead electrocardiogram and precordial 18 lead map, and second, instrumentation for hemodynamic measurements of direct arterial pressure, pulmonary capillary wedge pressure and cardiac output. All patients who did not meet the following hemodynamic criteria were excluded at this point: heart rate of 80 or more beats/min, mean arterial pressure of 75 or more mm Hg, wedge pressure less than or equal to 25 mm Hg and cardiac index of 2.5 or more liters/min per m^2. These limits were set to allow the administration of at least moderate doses of propranolol considering its known negative inotropic and chronotropic effects. The third measurement before initiation of therapy was a repeat electrocardiographic map and 12 lead electrocardiogram at the end of this 60 minute evaluation. A final group of patients was excluded if either ΣST_6 or $\overline{ST}$ had decreased more than 10 percent in 1 hour.

Protocol: Of 187 patients who entered the coronary care unit, 59 had anterior wall myocardial infarction, and 12 met all the criteria for entry into the study (Table I). The following protocol was carried out: Propranolol was infused intravenously at a rate of 1 mg every 2 minutes with continuous monitoring of direct arterial pressure, pulmonary capillary wedge pressure, heart rate and the standard precordial lead exhibiting maximal S-T segment elevation. Cardiac output was remeasured after infusion of each 2 mg of the drug. The target dose for beta adrenergic blockade in each patient was 0.15 mg/kg body weight, but the actual dose was determined by the hemodynamic response and drug administration was discontinued if the heart rate decreased to less than 60

ABLE I

atient Population

Case no.	Age (yr) & Sex	Site of Infarction	Hours From Onset of Infarction to Propranolol	Arrhythmias Before Propranolol
1	38M	Anterior	2.5	VPBs >10/min; VF X 3
2	53M	Anterior	5.5	VPBs >10/min; VF X 2
3	33M	Anterior	5.5	VPBs >8/min
4	48M	Anterior	2.5	VPBs >8/min; VF X 2
5	53M	Anterior	3	VPBs >2/min
6	57M	Anterior	2.5	VPBs >8/min
7	48M	Anterior	4	VPBs >3/min
8	47F	Anteroseptal	4	VPBs >3/min
9	38M	Anterior	7	VPBs >6/min
10	42M	Anteroseptal	6	VPBs >6/min
11	53M	Anterior	3.5	VPBs >8/min
12	41M	Anterior	2	VPBs >10/min

VF = ventricular fibrillation before the control period; VPBs = ventricular premature beats.

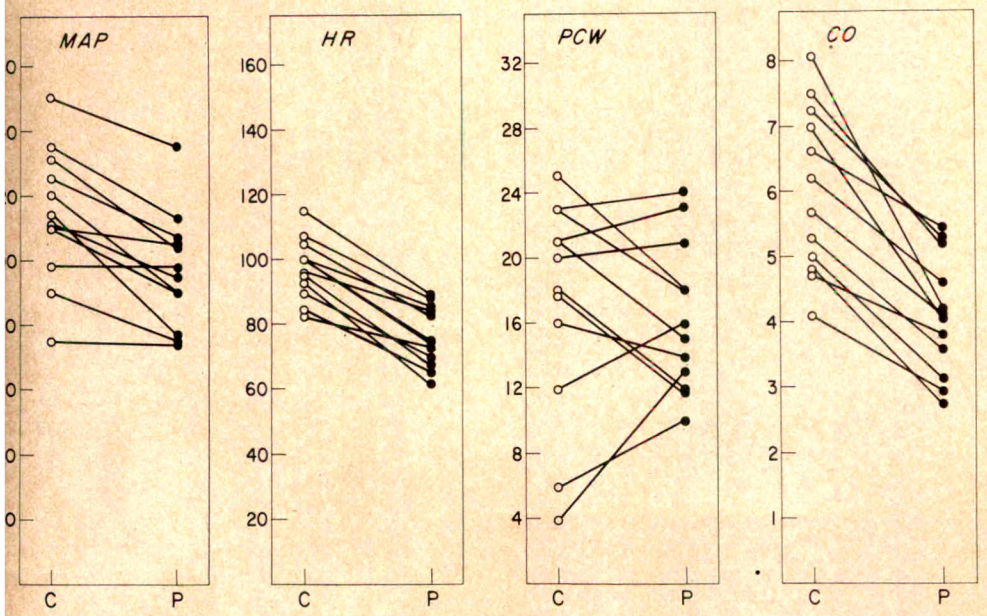


FIGURE 1. Hemodynamic effects of propranolol in patients with acute myocardial infarction before (C) and 30 minutes after intravenous administration (P). CO = cardiac output (liters/min); HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); PCW = mean pulmonary wedge pressure (mm Hg). All changes except those in mean pulmonary wedge pressure are significant.

beats/min or the cardiac index decreased to less than 2.0 liters/min per m^2. The average dose was 6.5 mg (range 3 to 10 mg).

The effect of the intravenous infusion of propranolol was observed by comparing the hemodynamic variables, precordial S-T elevation and subjective level of pain during the 1 hour control period with immediate changes in pain and in the continuously monitored precordial lead and with repeat measurements at 30 minutes and 4 hours. During the entire 5 hour period of study, the medical program was otherwise held constant with continuous administration of oxygen by nasal cannula and intravenous infusion of lidocaine at a rate of 2 mg/min. No patient received digitalis, insulin or potassium during or before the study. Three patients had received intravenous infusions of procainamide after ventricular fibrillation before entry into the study (Table I). No other arrhythmia, except for ventricular premature beats, was seen during the control hour.

S-T segment mapping was performed with an 18 lead precordial map consisting of three rows of six leads: V_1 to V_6 at the standard positions and leads taken one interspace above and below. All sites were marked to permit proper repositioning of the movable suction electrode. Tracings were calibrated at 1 mv = 10 mm with a paper speed of 25 mm/sec. S-T segment elevation was measured to the nearest 0.5 mm from the T-P segment to the J point. Maps were analyzed in random order without accompanying clinical data.

Before discharge, 10 of 12 patients underwent selective coronary angiography with the Sones technique. At the time of cardiac catheterization all were in clinically and hemodynamically stable condition.

Statistical analyses were performed with Student's *t* test for paired data.

Results

Hemodynamic changes: The hemodynamic changes in the 12 patients before and 30 minutes after intravenous infusion of propranolol are summarized in Table II and Figure 1. Mean arterial pressure decreased from 112 ± 6 (standard error of the mean) to 95 ± 5 mm Hg (P <0.001). Heart rate for the group decreased from 100 ± 3 to 79 ± 4 beats/min (P <0.001); in no patient was it less than 60 beats/min. Pulmonary capillary wedge pressure decreased in six patients and increased in the other six. For the entire group the wedge pressure was not significantly changed (17 ± 2 to 16 ± 1 mm Hg), and no patient had pulmonary congestion. Cardiac output decreased in all patients (average decrease from 6.1 ± 0.3 to 4.1 ± 0.3 liters/min, P <0.001). In three patients cardiac output decreased to 2.7, 2.9 and 3.2 liters/min

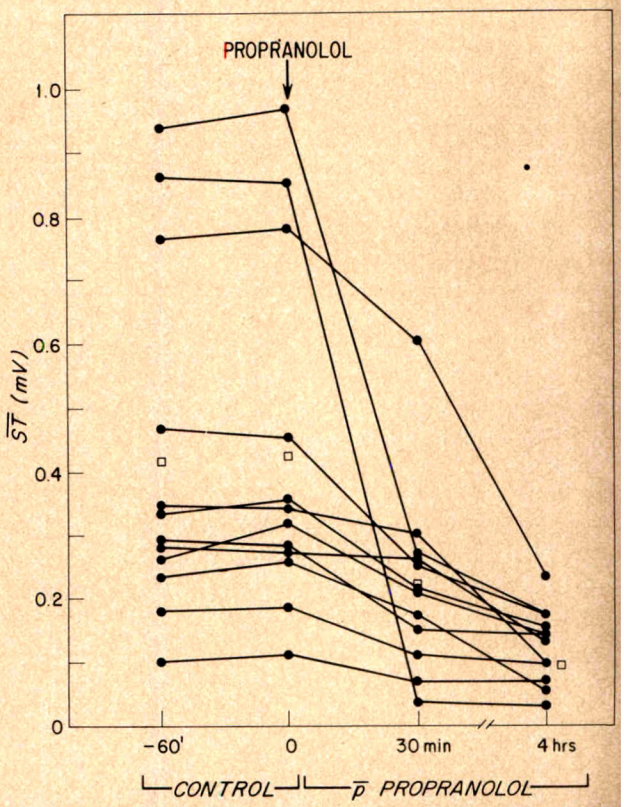


FIGURE 2. The effect of propranolol on average S-T segment elevatio ($\overline{ST}$) for each patient. $\overline{ST}$ remained unchanged during the 60 minut control period, but was significantly reduced 30 minutes after admir istration of propranolol. This reduction persisted 4 hours later. The ope squares represent mean values.

TABLE II

Hemodynamic Response to Intravenous Administration of Propranolol

Case no.	Control Data					Data 30 Minutes After Propranolol					Tota Dos (mg
	HR	MAP	PCW	CO	CI	HR	MAP	PCW	CO	CI	
1	93	110	23	7.2	3.4	62	90	18	5.2	2.5	5
2	90	110	21	4.8	3.2	70	100	15	2.7	1.8	3
3	107	114	12	4.1	2.6	88	77	16	2.9	1.8	4
4	115	130	16	8.1	4.1	88	104	14	4.2	2.1	10
5	85	135	6	6.2	3.1	65	113	10	4.6	2.3	5
6	95	90	18	5.3	2.9	68	75	12	3.6	2.0	4
7	103	120	25	7.5	3.6	83	90	18	5.3	2.5	10
8	100	75	18	5.7	2.9	75	75	12	4.2	2.2	10
9	100	125	20	5.5	2.8	85	107	21	3.8	2.0	5
10	95	98	4	6.6	3.4	85	98	13	5.4	2.6	10
11	100	150	21	7.0	3.4	75	135	23	4.1	2.0	6
12	110	83	23	5.0	2.7	105	78	24	3.2	1.7	6
Mean	100	112	17	6.1	3.2	79	95	16	4.1	2.1	6.5
± SE	± 3	± 6	± 2	± 0.3	± 0.1	± 4	± 5	± 1	± 0.3	± 0.9	± 0

CI = cardiac index (liters/min per m^2); CO = cardiac output (liters/min); HR = heart rate (beats/min); MAP = mean arterial pressure (m Hg); PCW = pulmonary wedge pressure (mm Hg); SE = standard error.

This decrease was transient and not associated with oliguria, acidosis, signs of cerebral hypoperfusion or an excessive reduction in arterial pressure. The decrease in cardiac output in each patient was directly related to dose. The maximal hemodynamic effects of propranolol were always noted within 30 minutes of the end of the infusion and dissipated within 4 hours.

Electrocardiographic changes: The average S-T segment elevation in the precordial maps ($\overline{ST}$) and the sum of S-T segment elevation in the six standard precordial leads (ΣST_6) did not decrease more than 5 percent in any patient during the control hour. $\overline{ST}$ for the group rose from 0.42 ± 0.08 to 0.43 ± 0.08 mv (Fig. 2) and average ΣST_6 rose from 26.0 ± 4.5 to 27.1 ± 4.3 mm (Table III). Thirty minutes after administration of propranolol there was a marked reduction in S-T segment elevation (Fig. 3). $\overline{ST}$ and ΣST_6 decreased in every patient. For the group $\overline{ST}$ decreased 39 percent, from 0.43 ± 0.08 to 0.22 ± 0.04 mv ($P < 0.02$) (Fig. 2), and ΣST_6 decreased 40 percent, from 27.1 ± 4.3 to 15.3 ± 3.3 mm ($P < 0.02$) (Table III). Thus, $\overline{ST}$ paralleled ΣST_6, showing that in this instance either variable could be used. The reduction in S-T segment elevation persisted for 4 hours after administration of propranolol although the hemodynamic effect dissipated. The maximal rate of reduction always was seen during the first 30 minutes after infusion of propranolol. Further, more gradual resolutions of S-T elevation continued despite decreasing beta blockade. These changes in S-T segment elevation were compared with those that occurred in seven other patients who met the same admission criteria but did not receive propranolol. In the untreated group, after the 1 hour control period that assured S-T segment stability, $\overline{ST}$ and ΣST_6 were measured 30 minutes and 4 hours later and showed no significant changes ($\overline{ST}$ increased by 0.03 ± 0.05 mv and ΣST_6 decreased by 0.01 ± 0.05 mv, respectively). Thus, the reduction in S-T segment elevations in the treated patients after administration of propranolol was not observed in a comparable group of patients who did not receive the drug.

The magnitude of S-T segment response to propranolol varied within a wide range (Fig. 2, Table III). Both good and poor responses were seen and could be related to the coronary angiographic findings, which also could be separated into two groups. All four patients with occlusion of the left anterior descending coronary artery without collateral flow had a reduction in ΣST_6 of less than 40 percent in 30 minutes (Fig. 4). All six patients with angiographically demonstrable flow to the infarcted area, either through significant stenosis of the left anterior descending artery or by way of collateral vessels, had a more than 40 percent reduction of ΣST_6.

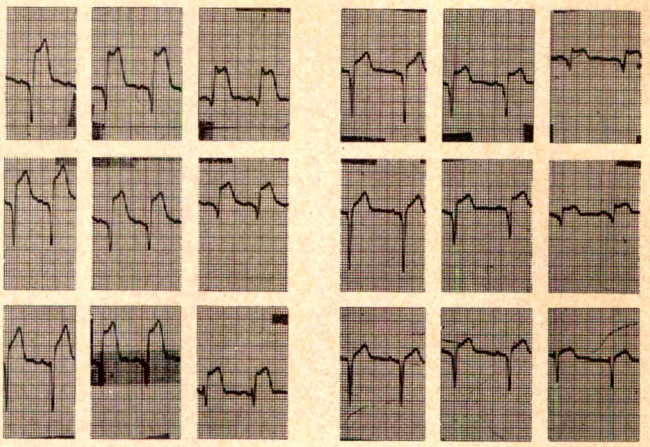


FIGURE 3. The effect of propranolol on the reduction in S-T segment elevation in an average patient. The nine leads depicted are from the V_1, V_3 and V_5 positions and the corresponding sites one intercostal space above and below the standard positions.

ABLE III

ffect of Intravenous Administration of Propranolol n Sum of S-T Segment Elevations in Six Standard Leads ΣST_6) (mv)

Case no.	60 Minutes Before Control	Control	After Propranolol 30 Minutes	After Propranolol 4 Hours
1	55.0	53.0	2.0	2.0
2	48.0	47.5	19.5	10.5
3	24.0	26.0	15.0	11.0
4	48.5	51.5	46.0	8.0
5	11.0	11.0	6.0	6.0
6	15.0	19.5	10.5	3.5
7	21.5	25.0	13.0	9.0
8	18.0	21.0	15.0	10.0
9	15.5	16.5	11.0	8.0
10	11.0	10.5	5.5	3.5
11	19.0	19.0	18.0	7.0
12	25.0	24.5	22.5	11.0
ean	26.0	27.1	15.3	7.5
±SE	± 4.5	± 4.3	± 3.3	± 0.9
value*	NS		<0.02	<0.02

*In reference to control data.
NS = not significant; P = probability; SE = standard error.

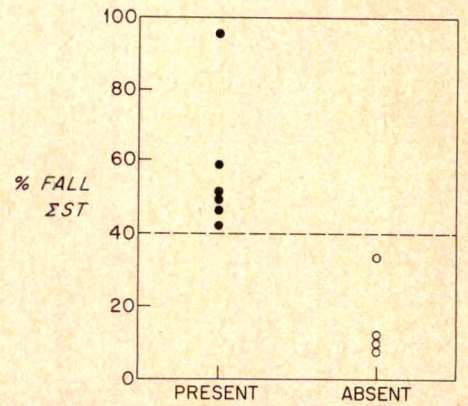


FIGURE 4. Relation between the degree of reduction in S-T segment level and the presence or absence of angiographically demonstrable flow in the infarcted zone. All patients with more than 40 percent reduction in the sum of S-T segment elevation from leads V_1 through V_6 (ΣST_6) in 30 minutes had flow to the area of infarction (closed circles). In contrast, in the four patients with no demonstrable flow angiographically (open circles), ΣST_6 decreased by less than 40 percent after administration of propranolol.

Clinical observations: Before administration of propranolol all patients had persistent pain (average grade 5/10) despite administration of oxygen and morphine (average dose 6.5 mg intravenously). In 9 of 12 patients, pain was relieved completely or reduced to grade 1/10 within 30 minutes of infusion of propranolol. In three patients (Cases 4, 11 and 12), pain persisted with a minimal reduction in intensity. These patients were the three with the poorest S-T segment response and an occluded left anterior descending artery without collateral vessels (Fig. 4). Ventricular ectopic beats decreased and ventricular fibrillation did not occur in any patient after beta adrenergic blockade. No patient manifested an atrioventricular conduction defect. Serial determinations of serum glutamic oxaloacetic transaminase (SGOT), creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) activity confirmed an acute myocardial infarction in all cases. Peak SGOT averaged 385 units (range 160 to 550), CPK, 1,034 units (range 525 to 2,220) and LDH 658 units (range 280 to 940). All patients survived and left the hospital.

Discussion

It has been postulated that during the first several hours after the onset of acute myocardial infarction in man, the necrotic process is a dynamic one affecting to various degrees the myocardial cells within the ischemic zone, resulting in a nonhomogeneous infarction.[7] Thus, during this early period, populations of normal, injured and necrotic myocardial cells coexist in the same regions.[8] The cells that are still in the phase of reversible injury and can either progress to necrosis or retain viability constitute the majority of the affected cells in the very beginning of the ischemic event and decrease in number with the passage of time and persistence of ischemia. If, during this time interval, a therapeutic measure could reverse the ischemic process of injury, the resulting extent of necrosis, that is, myocardial infarction, would be smaller. This conceivably would be of benefit since large infarctions have been associated with cardiogenic shock.[9]

Propranolol in experimental coronary occlusion: When a severe imbalance between myocardial oxygen requirement and delivery occurs, as is the case of a marked reduction in regional coronary flow, the process of myocardial damage is initiated.[10,11] To counteract it, oxygen imbalance must be improved either by ameliorating the inadequate coronary flow or by decreasing oxygen demand. This concept is now universally accepted in the treatment of angina pectoris in which therapy with beta adrenergic blockade has a prominent role.[2–4] However, its applicability in man with acute myocardial infarction is not well established. Experimentally in dogs, beta adrenergic blockade with propranolol reduced the extent of myocardial ischemic injury not only when administered as pretreatment but also when given as late as 3 hours after coronary occlusion.[5,6,12] Propranolol substantially reduced the coronary occlusion-induced S-T segment elevations in both the epicardium and the precordium.[5,12] The reduction of S-T segment elevation in each epicardial site predicted the prevention of myocardial CPK activity depression that occurs 24 hours after occlusion, thereby demonstrating that the electrical phenomenon of reduction in S-T segment elevation correlated well with the protection of the ischemic regions as judged by enzymatic criteria of myocardial damage.[5] Moreover Sommers and Jennings,[13] using histologic measurement, showed that propranolol minimized infarct size If reduction in S-T segment elevation were the only alteration after administration of propranolol, this decrease in the current of injury might be considered a nonspecific effect of propranolol, possibly due to its membrane effect. However, since propranolol unequivocally decreased the extent of myocardial damage as expressed by histologic appearance and myocardial CPK activity, it is more probable that the reduction of S-T segment elevation is indicative of a decrease in ischemic injury.

Assessment of ischemic injury in man: In man, the evaluation of ischemic injury must be restricted to less direct techniques that are imperfect by nature. Myocardial ischemic injury in the clinical setting can be assessed by: (1) level of pain; (2) ventricular irritability (3) alteration in lactate metabolism; (4) radionuclide scintigraphy by gamma or positron imaging of the myocardium; (5) release of enzymes from the injured myocardium (CPK disappearance curves); and (6) precordial S-T segment mapping. The evaluation of changes in lactate metabolism are closely dependent on sampling techniques and may be subject to errors in predominantly regional disease. The radionuclide techniques are of great potential applicability, but their use in monitoring changes in the extent of an ischemic zone awaits further developments.

Predicting "infarct size" with CPK disappearance curves requires a 10 hour delay in treatment and is therefore not applicable when therapy is indicated in the early hours of infarction. Pain is admittedly subjective, variable and not always ischemic in origin However, pressing precordial pain in the first 8 hours of infarction is probably ischemic in origin, and changes in intensity of pain over 30 minutes during an intravenous infusion of a nonanalgesic agent can be followed Ventricular irritability is related to ischemic injury although not in a quantitative way.

Although the use of precordial S-T segment elevations in patients does not permit quantitative evaluation of the size of an infarction, it is a useful technique for assessing directional changes in myocardial ischemic injury.[12] This view is based on the observations that precordial electrocardiograms provide semidirect measurements of epicardial events[14,15] and that interventions that change the extent and magnitude of S-T segment elevations induce parallel alterations in S-T segment elevation in the canine precordium and epicardium.[16] Experimentally, epicardial S-T segment elevation correlates well with reduction in myocardial partial pressure of oxygen,[17,18] reduction in coronary flow and production of lactate,[19] local changes in the high energy phosphate and lactate[20] and with myocardial CPK activity[6]; most importantly it predicts accu

rately the areas of necrosis as defined by light and lectron microscopy.[21]

To establish the effects of propranolol using the precordial electrocardiographic method, it was necesary to include in the study only a small fraction of paients who entered the coronary care unit. Thus, only patients with unquestionable acute transmural myocardial infarction of the anterior wall were included since not all other patients are suitable for precordial mapping. All patients were required to have both clinical (opiate-resistant ischemic pain and arrhythmias) and electrocardiographic signs of persistent ischemic injury as reflected by stable S-T segment elevation, and all patients whose S-T segment level decreased spontaneously during the period of observation were excluded from the study. The exclusion of all patients with infarction older than 8 hours was carried out to maximize the possible effects of treatment since the number of myocardial cells in the reversible phase of injury is greatest in the early hours of infarction; later treatment can be aimed mainly at preventing extension of infarction. Patients were also excluded if they showed changes in the duration of the QRS complex with S-T segment changes of nonischemic origin.

Effect of propranolol on S-T segment elevations: After the intravenous administration of propranolol, the decrease in S-T segment elevation was accompanied by other signs of reduction of ischemia, namely, pain and ventricular arrhythmias. The change in S-T segment elevation in the multiple leads and in the six precordial leads was directionally similar, indicating that when a change of this magnitude occurs even a single lead may be adequate to register the alteration, although multiple lead systems may be more sensitive to small decrements. These observations are in accord with the findings of Mueller et al.[22] who showed the beneficial effect of propranolol on the metabolic variables of the ischemic heart in patients with acute myocardial infarction.

The response of S-T segment elevation to propranolol appeared to be related to the presence or absence of angiographically demonstrable flow to the infarcted zone. The patients with flow to the infarcted territory had a more complete resolution of myocardial injury. This response may be related to the ability of propranolol to enter the zone of infarction and affect the still viable cells within the ischemic area. In contrast, in the patients without flow to the artery distal to the occlusion, the beneficial effects of propranolol on reduction of S-T segments were less marked since the drug probably could not penetrate the ischemic zone and its action was therefore confined to the ischemic periinfarction area. In addition, more complete resolution of the current of injury might have been possible in some patients if larger doses of propranolol had been tolerated. However, the administration of additional propranolol was limited by the reduction in cardiac output.

Hemodynamic monitoring of action of propranolol: Since propranolol may have a deleterious effect on myocardial function in patients with acute myocardial infarction, its hemodynamic effects were continuously monitored. The two most important hemodynamic responses to propranolol in these patients were decrease in cardiac output and reduction in heart rate. The degree of myocardial depression resulting from beta adrenergic blockade was well tolerated in all patients as evidenced by adequate organ and peripheral perfusion throughout the period of drug effect. Furthermore, pulmonary capillary wedge pressure did not increase systematically, and no patient had pulmonary congestion.

The use of propranolol in acute myocardial infarction has been thought to be contraindicated because there have been reports[23,24] of adverse reactions after its intravenous administration in acutely ill patients in intensive care units. However, our data indicate that this agent can be safely administered in the early hours of myocardial infarction when patients are categorized hemodynamically before drug administration and those with marginal circulatory dynamics are excluded. Furthermore, repeated hemodynamic measurements permit titration of the dose to the maximal tolerated levels, thus avoiding unwarranted side effects.

In summary, judicious intravenous administration of propranolol to patients in the early phase of acute myocardial infarction reduced the signs of ischemic injury. This therapeutic approach, which aims directly at the interruption of ischemic injury, may play an important role in the management of these patients.

Acknowledgment

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Propranolol Therapy in Patients Undergoing Myocardial Revascularization

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The records of 185 consecutive patients having myocardial revascularization were reviewed with regard to preoperative administration of propranolol and intraoperative or postoperative complications. Tachycardia and hypertension before cardiopulmonary bypass were slightly more common in patients never taking propranolol or those who had discontinued it for more than 48 hours before operation. There was no statistically significant difference in the incidence of postbypass hypotension among patients who took propranolol within 24 hours of operation, those who discontinued it more than 24 hours before operation, and those who never took the drug. Operative mortality was not significantly different among patients who received propranolol within 48 hours of operation (3 percent), those who never took it and those who discontinued it more than 48 hours before operation (4 percent). Early in the series, five patients had an acute myocardial infarction within 48 hours after routine preoperative withdrawal of propranolol. Because complete withdrawal of propranolol in patients with unstable angina pectoris may lead to acute myocardial infarction, we recommend gradual withdrawal of the drug during 48 hours before operation. If this is not possible because anginal pain recurs or intensifies, then reduced doses may be given safely up to 10 hours before revascularization, provided that the patient is a satisfactory candidate for bypass and that adequate myocardial revascularization can be accomplished.

The beta adrenergic receptor blocking agent propranolol has greatly enhanced the medical management of patients with angina pectoris. It is probable that its mechanism of action is the reduction of tissue oxygen requirements to levels that can be supplied by the existing arterial circulation. This reduction in myocardial oxygen consumption is achieved primarily by depression of myocardial contractility and reduction in heart rate.[1–3] Because the drug is known to have a depressive action, some authors[4] have stressed that it should be discontinued at least 2 weeks before anticipated myocardial revascularization to avoid increased morbidity and mortality in the early postoperative period. However, in many patients, particularly those with very unstable angina, withdrawal of propranolol for even short periods may exacerbate symptoms and lead to acute myocardial infarction before revascularization.[5–7] To determine if there were recognizable adverse effects of the drug either before or after cardiopulmonary bypass, 185 consecutive patients undergoing myocardial revascularization were analyzed with regard to preoperative administration of propranolol and intraoperative or postoperative complications.

Methods

One hundred eighty-five consecutive patients undergoing myocardial revascularization between July 1973 and July 1975 were classified into four groups according to the interval between discontinuation of propranolol and induction of anesthesia. Patients in Groups I to III had discontinued propranolol less than

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24 hours, 24 to 48 hours and more than 48 hours, respectively, before induction of anesthesia. Patients in Group IV had never taken propranolol.

The four groups were analyzed for age, dose of propranolol, pattern of anginal pain, presence of preoperative myocardial infarction, preoperative left ventricular function, number of coronary arterial bypass grafts and development of perioperative infarction as demonstrated by electrocardiographic evidence of new Q waves of 0.04 second's duration.[8] Unstable angina pectoris was defined as the recent onset of pain or a change in the pattern of pain or to include one of the following subsets: progression of previously stable angina on effort occurring with minimal provocation; pain at rest associated with disabling effort angina; or prolonged episodes of pain without infarction. Electrocardiographic changes occurring in the hospital were not required for assignment to the category of unstable angina.[9]

Complications were evaluated before and after cardiopulmonary bypass. Complications before cardiopulmonary bypass included episodes of bradycardia, tachycardia, hypotension or hypertension occurring before or after induction of anesthesia. Hypotension was defined as systolic blood pressure 20 percent below the lowest recorded preoperative pressure, and hypertension as systolic pressure 20 percent above the highest recorded preoperative pressure. Bradycardia was defined as a heart rate of less than 50 beats/min, and tachycardia as a rate of more than 120 beats/min. If hypotension occurred after cardiopulmonary bypass, patients were classified into those needing inotropic support with sympathomimetic agents and those requiring counterpulsation with the intraaortic balloon pump. Patient mortality was defined as all postoperative deaths occurring in the hospital. Complications possibly due to preoperative discontinuation of propranolol were also evaluated. Statistical significance was determined with chi square analysis.

The anesthetic technique used for all patients consisted of induction with morphine and diazepam and maintenance with 50 percent nitrous oxide, oxygen, morphine, pancuronium and 0.5 to 2 percent enflurane as required. In some cases thiopental supplemented the induction agents. The average doses were morphine sulfate, 0.3 to 0.5 mg/kg; diazepam, 0.2 to 0.3 mg/kg; pancuronium, 0.1 mg/kg; and thiopental, 50 to 100 mg.

Results

Clinical characteristics of patients preoperatively: Of the 185 patients in the series, 113 (61 percent) received propranolol within the 48 hours before operation (Groups I and II) (Table I); 159 (86 percent) were taking propranolol at some time before myocardial revascularization. More patients in Group I (propranolol

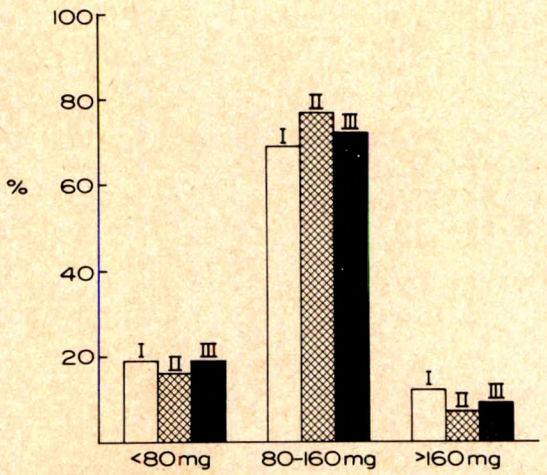


FIGURE 1. Percent of patients in Groups I, II and III receiving various daily doses of propranolol. Group I had the most patients taking more than 160 mg/day. Chi square analysis revealed no significant difference among groups.

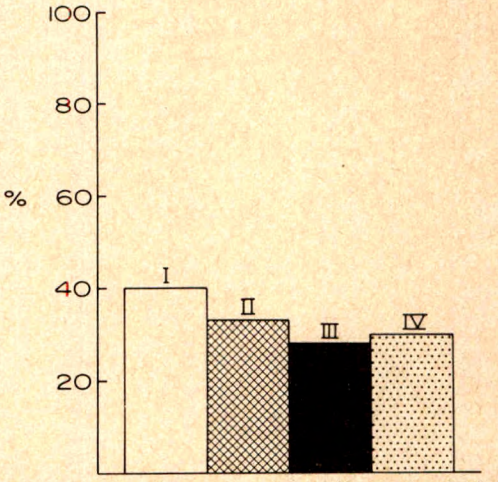


FIGURE 2. Percent of patients with preoperative myocardial infarctio as evidenced by presence of Q waves in the electrocardiogram. Th finding was more prevalent in patients in Group I, but chi square analys revealed no significant difference among groups.

TABLE I

Characteristics of 185 Patients Undergoing Coronary Arterial Bypass Grafting

Group*	Patients (no.)	Propranolol Administration: Daily Dose (mg) Mean	Daily Dose (mg) Range	Hours Since Last Dose	Mean Age (yr)	Total Bypass Grafts (no. of patients) 1	2	3	4	Grafts Per Patien (no.)
I	51	129	20–320	<24	51	12	21	16	2	2.16
II	62	135	40–480	25–48	52	10	28	20	5	2.35
III	46	117	40–320	>48	50	8	26	10	1	2.04
IV	26	. . .	. . .	Never taken	48	11	11	2	2	1.81
All groups	185	127	20–480		51	41	86	48	10	2.09

*Groups I to IV are defined according to interval between last dose of propranolol and induction of anesthesia.

within 24 hours of operation) were taking the larger doses of the drug, although there was no statistical difference among the four groups (Fig. 1). The mean age in the series was 51 years (range 38 to 69 years). There was no significant age difference among groups although patients in Group IV (never given propranolol) tended to be slightly younger. One hundred fifty-nine patients (86 percent) were men; 26 were women.

One hundred fifty-five patients (84 percent) had unstable angina as defined, and 94 of the 155 (61 percent) were classified in Group I or II. Previous myocardial infarction as defined by the presence of Q waves of 0.04 second's duration was slightly (20 of 51 patients, 39 percent) more prevalent in Group I than in the other groups, but the differences among groups were not statistically significant (Fig. 2).

In general, there was little correlation among the various indexes of preoperative left ventricular function among the groups although patients in Group II had more impairment (elevated left ventricular end-diastolic pressure, depressed ejection fraction) than the other groups (Fig. 3). There was no significant difference in preoperative left ventricular function between patients who received propranolol within 24 hours of operation and those who never took the drug.

Number of bypass grafts: Although the severity of coronary artery disease was not necessarily related to the number of bypass grafts performed, aortic cross-clamp and durations of myocardial ischemia were correspondingly longer in patients receiving more grafts. Triple coronary arterial bypass grafting was performed most frequently in Groups I and II (36 of 113 patients) and least often in Groups III and IV (12 of 72 patients) (Table I). The number of coronary bypass grafts per patient was greater for patients who had received propranolol within 48 hours of operation (Groups I and II) than for patients who had no propranolol for more than 48 hours before operation (Group III) or patients who never took the drug (Group IV).

Preoperative complications: The total incidence of complications before cardiopulmonary bypass was not greatly different among the four groups although hypotension was significantly more frequent among patients in Group II (Fig. 4). Hypertension and tachycardia tended to occur slightly more frequently in patients who never took propranolol.

Postoperative complications: The incidence of complications after cardiopulmonary bypass was statistically no greater in patients who received propranolol within 48 hours of operation than in those who either had never taken the drug or had discontinued it for more than 48 hours before operation (Fig. 5).

Hypotension and decreased cardiac output sufficient to justify the intraaortic balloon pump were present in two patients, both classified in Group I. Both patients had satisfactory preoperative left ventricular function, and postoperative cardiac catheterization revealed little change in ejection fraction from preoperative values. Of the four grafts in these two patients, three were patent at restudy. There seemed to be no adequate explanation for these patients' depressed left ventricular function after cardiopulmonary bypass but, since both received propranolol within 24 hours of revascularization, it is possible there may have been some transient myocardial depression due to the drug.

Bradycardia after cardiopulmonary bypass was not a significant problem in any group because it occurred in only 4 of the 185 patients. The reduced heart rate was easily managed in all four patients.

Mortality: There was no difference in operative mortality between patients who received propranolol within 24 hours of operation and those who never had the drug (Fig. 5). Of the six patients in the series who died (3.2 percent), three were in Group II and three in

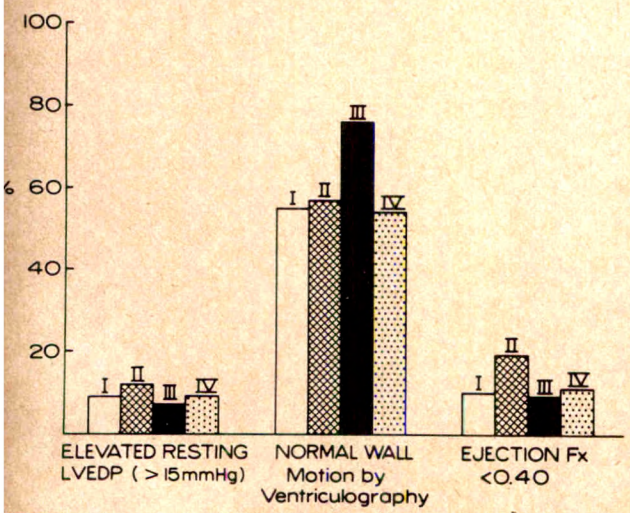


FIGURE 3. Percent of patients with various indexes of left ventricular function preoperatively. Dysfunction was most prevalent in patients in Group II as demonstrated by chi square analysis. Fx = fraction; LVEDP = left ventricular end-diastolic pressure.

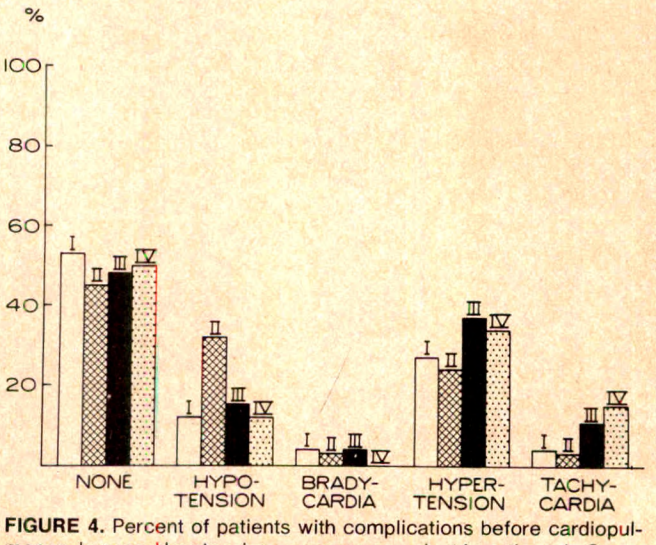


FIGURE 4. Percent of patients with complications before cardiopulmonary bypass. Hypotension was more prevalent in patients in Group II. Hypertension and tachycardia were slightly more common in patients who discontinued propranolol more than 48 hours before bypass (Group III) and in those who never took propranolol (Group IV).

Group III (Table II). The presence of a pattern of unstable angina did not increase operative mortality. Although unstable angina was present preoperatively in four of the six patients who died, this finding was anticipated because 84 percent (155 of 185) of the entire series had a pattern of unstable angina.

Myocardial infarction: Serial preoperative and postoperative electrocardiograms were available for comparison in 164 patients. New Q waves were present in 11 patients, indicating a perioperative infarction rate of 6.7 percent. There was no correlation between the development of new Q waves and previous myocardial infarction, number of coronary arterial bypass grafts performed, preoperative bradycardia or tachyarrhythmias or inotropic support in the postoperative period. There was no statistically significant difference in the incidence of perioperative infarction between patients who took propranolol within 24 hours of revascularization (2 of 47) and those who discontinued the drug more than 48 hours before operation (2 of 39).

Five patients had an acute myocardial infarction within 48 hours of withdrawal of propranolol therapy in anticipation of scheduled coronary bypass surgery. Two of these five patients died; the other three recovered with medical therapy.

Discussion

Duration of effects of propranolol after discontinuation: Because of known myocardial depressant activity of propranolol, some investigators[4] have incriminated it as a contributor to the low cardiac output state occasionally seen after coronary bypass surgery and have recommended that it be discontinued 2 weeks before operation. Others[10,11] have failed to substantiate the adverse effects of propranolol. Clinical and experimental studies[12,13] demonstrated that in man propranolol had a half life of 3.4 to 6 hours after discontinuation of its long-term administration. Furthermore, the drug could not be detected in samples of plasma and tissue (left atrium) 36 to 48 hours after its withdrawal. Plasma and heart concentrations decreased at the same rate, thus negating the concept of a long-lasting pool of drug in the myocardium. Therefore, on purely pharmacologic grounds, the authors of these studies[12,13] recommended a withdrawal time of 36 to 48 hours as sufficient for complete recovery from the cardiac effects of propranolol or any active metabolites. Our previous studies[14] showed the absence of measurable hemodynamic effects of propranolol 24 to 48 hours after its discontinuation.

More recently, Romagnoli and Keats[15] described 34 patients who discontinued propranolol 18 to 48 hours before myocardial revascularization. Although these workers detected propranolol in the plasma and atrial tissue of a significant number of these patients, they found no difference in blood pressure and heart rate response to a test dose of isoproterenol between these patients and patients never given propranolol. They concluded that no effective beta blockade was present 18 hours after acute preoperative withdrawal of propranolol in patients taking up to 300 mg/day.

Our clinical experience with 113 patients taking propranolol within 48 hours of myocardial revascularization substantiates these studies. We found no more complications before or after cardiopulmonary bypass in these patients than in those who never took propranolol or discontinued it more than 48 hours before operation. Important factors such as dose of propranolol, previous myocardial infarction, preoperative left ventricular function and intraoperative myocardial depression after aortic cross-clamping were not weighed in favor of patients in Groups I and II (discontinuation of propranolol less than 24 hours and 24 to 48 hours respectively, before induction of anesthesia). In fact doses of propranolol were larger, and preoperative

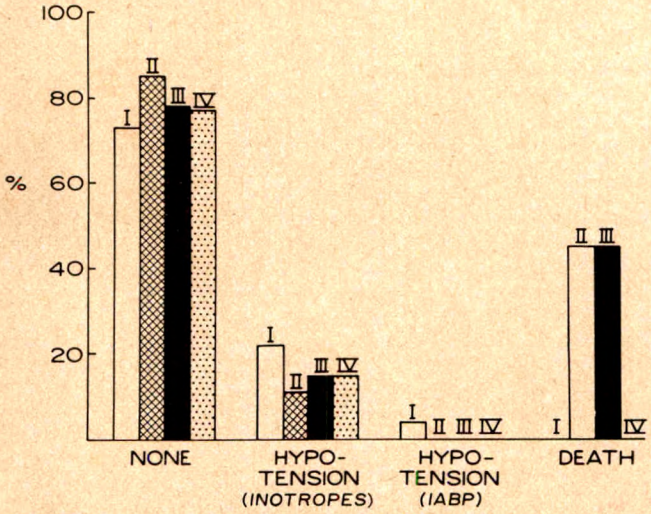


FIGURE 5. Percent of patients with complications after cardiopulmonary bypass. Incidence of hypotension requiring inotropic drugs (inotropes) was not significantly greater in patients receiving propranolol less than 24 hours before operation. There was no statistically significant difference by chi square analysis. Mortality rates were no different between Groups I and IV. Of the six deaths that occurred, three (50 percent) were in Group II and three (50 percent) in Group III. IABP = intraaortic balloon pumping.

TABLE II

Cause of Death in 6 of 185 Patients Undergoing Coronary Arterial Bypass Grafting

Case no.	Group	Cause of Death
1	III	Hypertensive episode; acute aortic dissection during cardiac catheterization 10 days after operation
2	II	Bilateral pseudomonas pneumonia
3	II	Low output immediately after operation
4	III	Massive pulmonary embolus 10 days after operation
5	III	Sudden ventricular arrhythmia; cardiac arrest 5 days after operation
6	II	Hypertensive episode; acute aortic dissection 7 days after operation

Group II = propranolol discontinued 25 to 48 hours before induction of anesthesia; Group III = propranolol discontinued more than 48 hours before induction of anesthesia.

ventricular dysfunction and the number of bypass grafts performed greater in the patients who received propranolol within 48 hours of operation.

Recommendations for preoperative propranolol therapy: When patients with unstable angina taking propranolol are admitted for elective myocardial revascularization we now reduce the drug dose progressively over the 48 hours before induction of anesthesia, if there has been no recent change in the pattern of anginal pain. If pain intensifies or recurs after the dose of propranolol has been reduced, reinstitution of effective drug levels is begun without hesitation. We have found that in most patients administration of propranolol can be tapered over this 48 hour period with the last dose given 10 hours before induction of anesthesia.

We have also noticed that patients taking propranolol within 48 hours of revascularization come to the operating room with a slower heart rate and less hypertension than patients who discontinue propranolol more than 48 hours before operation. This reduction in the rate-pressure product may have a beneficial effect in producing a corresponding decrease in myocardial oxygen consumption and ischemia in certain unstable situations. Troublesome bradyarrhythmia or hypotension has not occurred in these patients. The anesthetic management is extremely important in avoiding pre- or postoperative complications. Episodes of extreme hypotension, hypertension or tachycardia in the periods before and after cardiopulmonary bypass must be avoided by careful titration of anesthetic drugs.

Evidence of transmural myocardial infarction in the perioperative period has been reported in 6 to 40 percent of patients.[16–19] Its mechanism of production is presently unknown and is not necessarily related to graft failure.[20] No conclusions can be drawn from our data with regard to a protective or deleterious effect of propranolol on the incidence of perioperative infarction.

Clinical implications: In our experience propranolol therapy within 48 hours of operation does not increase the incidence of complications before or after cardiopulmonary bypass. Propranolol therapy in the manner described does not increase the morbidity or mortality of the operative procedure. However, complete withdrawal of propranolol in patients with pattern of unstable angina may often lead to unexpected acute myocardial infarction or death before operation. We recommend administration of propranolol be tapered during 48 hours before operation. If this is not possible, then propranolol may be given safely up to 10 hours before revascularization provided that the patient is a satisfactory candidate for bypass and that adequate myocardial revascularization can be accomplished.

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Effect of Lithium on Cardiovascular Performance: Report on Extended Ambulatory Monitoring and Exercise Testing Before and During Lithium Therapy

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To assess the effect of long-term lithium therapy on cardiac arrhythmia and cardiovascular performance, extended ambulatory electrocardiographic monitoring was performed in 12 patients, and rest and exercise electrocardiograms in 10 of 12, before and during lithium therapy. Lithium increased the frequency of premature ventricular contractions in three patients, decreased it in one, and produced no change in eight. Three of four patients with atrial arrhythmias showed improvement during lithium therapy. Exercise performance was unchanged. Although 7 of the 12 patients manifested T wave flattening in the resting electrocardiogram, none had S-T segment displacement at rest or on treadmill exercise. Before lithium therapy, arrhythmias on exercise included premature atrial contractions in four patients, ventricular arrhythmias in four (premature ventricular contractions in four, with couplets in two and with ventricular tachycardia in one). During lithium therapy, exercise did not provoke premature atrial contractions or ventricular tachycardia in any of the patients, but three patients had premature ventricular contractions (with couplets in one case).

We conclude that lithium at therapeutic levels *may* precipitate or aggravate ventricular arrhythmias. When administered to patients with heart disease, factors that interfere with renal clearance of lithium (heart failure, salt restriction, long-term diuretic therapy) must be recognized and doses must be adjusted accordingly. Careful follow-up and electrocardiographic monitoring are advisable if lithium is to be used in the presence of ventricular arrhythmias. Cardiovascular performance as assessed by treadmill exercise testing was not affected by long-term lithium therapy.

Lithium was introduced into psychiatric pharmacology in 1949,[1] but did not receive widespread attention until the last decade. Numerous studies in the past 10 years have established lithium as a valuable agent in the treatment of mania and for the prevention of a relapse in bipolar manic-depressive illness.[2] Beneficial results of lithium have also been reported in various other psychiatric disorders, but its value in disorders other than manic-depressive psychoses remains controversial.[3]

The presence of cardiovascular disease and arrhythmias is generally considered a contraindication to the use of lithium,[4,5] but a search of the literature reveals contradictory and inconclusive reports.[6] Many psychiatric patients with cardiac disease or arrhythmias have now been exposed to this drug. This study was designed to evaluate the effects of therapeutic doses of lithium on cardiac arrhythmias, exercise performance and the exercise electrocardiogram.

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Methods

Patient Population

Twelve patients, 11 men and 1 woman, with various psychiatric diagnoses were studied (Table I). Only adult patients who were able to give informed consent and whose attending psychiatrist considered them a candidate for lithium therapy were included in the study. Severely agitated patients or those in whom a 48 hour delay in therapy was deemed deleterious were excluded. Patients receiving long-term treatment with other medications were accepted if no change in dose was made during the study period. No attempt was made to exclude patients with known preexisting heart disease or arrhythmias.

Studies

All patients were examined by one of us (A.T.) and gave informed consent. The study was approved by the Stanford University School of Medicine and the Palo Alto Veterans Administration Hospital Committees on the Use of Human Subjects in Research. All patients underwent the following studies before lithium administration: complete blood count, urinalysis, determinations of serum creatinine, sodium, potassium, chloride and carbon dioxide, evaluation of thyroid function, chest X-ray and electrocardiogram. Exercise electrocardiography in 10 of the 12 patients and 42 to 48 hour ambulatory electrocardiographic monitoring in all patients immediately preceded administration of lithium.

Lithium carbonate was given orally, as prescribed by the attending psychiatrist, in daily divided doses ranging from 900 to 1,500 mg (24 to 40 mEq lithium/day). Serum levels of lithium were measured three times weekly. When these reached therapeutic levels (0.6 to 1.5 mEq/liter) in 6 to 14 days, 24 to 48 hour ambulatory electrocardiographic monitoring, exercise electrocardiogram and laboratory testing were repeated. Blood for serum lithium and other electrolyte determinations was drawn in the fasting state. Lithium levels were determined by atomic absorption spectrophotometry using a Perkin-Elmer No. 303 analyzer.

Arrhythmia detection: Ambulatory electrocardiographic monitoring was continued in four patients for 8 to 10 days without interruption, in two of these patients (Cases 11 and 12) because of preexisting severe coronary artery disease with arrhythmias and in the other two (Cases 9 and 10), because frequent premature ventricular contractions were noted on the initial examination. Except for Patients 11 and 12, who were restricted to a cardiac surveillance unit for added protection, all patients continued their usual level of unrestricted activity.

The 12 lead electrocardiogram was obtained with the patients supine in the postabsorptive state with use of a single channel Hewlett-Packard no. 1511 electrocardiograph. The ambulatory tracings were recorded using a single channel Avionics electrocardiographic tape recorder and a modified V_1 lead system. The patients recorded a detailed diary of symptoms and activities, including sleep, as they followed their normal daily routine. The tapes were processed at 60 times real-time, using a digital computer system developed at Stanford Medical Center.[7] This system provides plots of R-R interval, QRS duration and mean QRS vector for each heartbeat during the entire recording. These data are plotted simultaneously as a function of time, allowing visual detection of all arrhythmias. Verification of arrhythmias is made by sampling a digitized electrocardiographic signal from unlimited numbers of 1 minute segments of the recording. These segments are selected after visual inspection of the plots of R-R interval, QRS duration and mean QRS vector. Frequent or continuous sampling is made when there is a noisy signal or when there are complex arrhythmias. The entire record was divided into 1 hour segments and the total number of premature atrial or ventricular contractions per hour was determined by visual inspection of the computer-generated plots. The presence of multiform premature ventricular contractions, early (R on T) contractions, couplets, bigeminy and ventricular or supraventricular tachycardias was noted for each 24 hour recording. From the patient's diary the recording was divided into waking and sleeping periods, and each period was analyzed separately. In each patient the data obtained before treatment with lithium were compared with those obtained when lithium blood levels were in the therapeutic range.

Exercise electrocardiogram: The test was performed on a motorized treadmill and followed the protocol of Bruce and Hornsten[8] (Patients 2 and 3 refused this test). Leads II and

TABLE I
Clinical Status of Patients Before Lithium Therapy

Case no.	Age (yr) Sex	History of Heart Disease	Abnormal Cardiac Findings	Chest X-Ray Data	ECG Data	Other Medications
1	34F	None	None	Normal	Normal	
2	56M	None	None	Normal	Normal	Haloperidol, 20 mg/day
3	73M	HBP, CHF PAT	Bilateral rales; S_3 gallop; pedal edema	Cardiomegaly	ST↓	Digoxin, 0.25 mg/day; furosemide, 40 mg/day; haloperidol, 6 mg/day
4	51M	None	None	Normal	Normal	
5	42M	HBP	None	Normal	Normal	Hydrochlorothiazide, 50 mg/day
6	60M	PAT	None	Normal	Normal	Digoxin, 0.25 mg/day
7	54M	None	None	Normal	Normal	Diphenhydramine, 200 mg/day
8	57M	None	Mild AI	Normal	Normal	Diphenylhydantoin, 300 mg/day; chlorpromazine, 300 mg/day
9	51M	None	PCs	Normal	PVCs	. . .
10	25M	None	PCs	Normal	PVCs	. . .
11	64M	MI, VT	PCs, S_4 gallop	Cardiomegaly	PVCs, Ant MI	. . .
12	50M	MI, Angina	PCs, S_4 gallop	Cardiomegaly	PVCs, Ant MI	Tolbutamide

AI = aortic insufficiency; Ant = anterior; CHF = congestive heart failure; ECG = electrocardiographic; HBP = high blood pressure; MI = myocardial infarction; PAT = paroxysmal atrial tachycardia; PCs = premature contractions; PVCs = premature ventricular contractions; ST↓ = S-T segment depression; VT = ventricular tachycardia.

V_5 were monitored. On the initial test (before administration of lithium), patients were urged to perform maximally, and the tests were stopped at the request of the patient. On the second test (during lithium therapy) patients were encouraged to achieve the same level of exercise (in seconds) but were not permitted to exceed this level. No test was discontinued because of arrhythmia. Blood pressure was measured by a sphygmomanometer, with the patient standing, before and immediately after the exercise. The electrocardiogram was monitored continuously, and recordings of 20 seconds' duration were obtained every minute of exercise and for 8 minutes of the recovery period. All premature beats occurring during exercise or the first 8 minutes of recovery were counted and recorded for every 100 sinus beats.

Mathematical and statistical analyses were performed on a Hewlett-Packard model 9100A calculator, using standard programs. The mean number of premature ventricular and atrial contractions before and during lithium therapy was compared using a standard two-tailed *t* test.

Results

Clinical Course

Relevant clinical information is summarized in Table I. Before lithium therapy, four patients (Cases 1, 2, 4 and 7) were completely free of detectable heart disease. Two patients (Cases 9 and 10) had frequent premature ventricular contractions but no other detectable abnormalities noted in extensive noninvasive studies, including a maximal treadmill electrocardiographic test and echocardiograms, carefully searching for mitral valve prolapse. Three patients (Cases 5, 6, and 8) had mild abnormalities detected by history or physical examination but remained free of symptoms. Three patients (Cases 3, 11 and 12) had advanced coronary artery disease with a history of myocardial infarction, stable angina, congestive heart failure and short bursts of ventricular tachycardia.

During lithium therapy: Cardiac effects such as symptomatic arrhythmias, worsening angina or heart failure were not demonstrated by any patient during lithium therapy. Because serum lithium levels were monitored closely, no patient had lithium toxicity, although three were on a salt-restricted diet and two were receiving long-term diuretic therapy.

Electrocardiogram

Resting electrocardiogram: Changes in the 12 lead tracing during lithium therapy were minor and limited to T wave changes. Seven patients had 1 mm or more of T wave depression or flattening, and five showed no change. No T wave changes were seen in the patients with severe cardiac disease (Cases 3, 11 and 12), all of whom began the study period with an abnormal electrocardiogram.

Ambulatory monitoring: Table II summarizes the number of hours of ambulatory electrocardiographic monitoring during waking hours and sleep, and serum electrolytes and lithium levels during the ambulatory monitoring period for each patient. The duration of monitoring ranged from 27 to 74 hours (mean 42 hours) before lithium therapy and from 16 to 193 hours (mean 62 hours) during therapy. Serum electrolytes were normal and showed no significant change during lithium therapy. The number of days of lithium therapy before repeat ambulatory electrocardiographic monitoring ranged from 6 to 14. Serum lithium levels during the period of monitoring were in the therapeutic range of 0.8 to 1.4 mEq/liter (mean 1.2 mEq/liter) for all patients. In Patients 9 through 12, who were monitored continuously during the 6 to 8 days of lithium administration, peak serum lithium levels ranged from 1.1 to 1.4 mEq/liter.

Ventricular Arrhythmias

During the entire study period, all patients except one (Case 5) had some ventricular arrhythmia. In five patients (Cases 1, 2, 4, 6 and 8) the arrhythmia was limited to isolated rare premature ventricular contractions ranging in frequency from 1 to 7/day, with no change during lithium administration. These patients were considered to be free of significant arrhythmia and were excluded from further analysis. Five of the remaining six patients had frequent premature ventricular con-

TABLE II

Duration of Ambulatory Electrocardiographic Monitoring and Serum Electrolyte and Lithium Levels Before and During Lithium Therapy

Case no.	Before Lithium Therapy: Hours of ECG	Serum (mEq/liter) K+	Na+	Cl−	CO_2	During Lithium Therapy: Days of Therapy	Hours of ECG	Serum (mEq/liter) K+	Na+	Cl−	CO_2	Li+
1	32A; 14S	4.0	139	106	27	14	30A; 14S	4.3	141	104	24	1.3
2	20A; 8S	3.9	141	101	25	10	10A; 6S	4.1	140	99	24	1.4
3	32A; 14S	4.8	137	97	33	8	9A; 8S	4.3	139	99	30	0.9
4	29A; 18S	4.4	139	101	22	14	21A; 22S	4.6	143	107	25	0.9
5	28A; 9S	4.4	143	104	25	14	27A; 19S	4.7	144	102	26	1.3
6	21A; 13S	4.8	140	98	31	10	22A; 12S	4.8	141	98	29	1.4
7	14A; 13S	4.5	137	97	20	6	20A; 18S	4.7	140	102	22	1.2
8	25A; 18S	4.3	137	97	18	10	25A; 16S	3.8	136	98	20	0.8
9	50A; 24S	4.3	140	105	21	6	67A; 33S	4.7	140	99	24	0.3–1.1
10	23A; 19S	4.4	140	102	30	8	135A; 58S	4.7	143	102	31	0.3–1.1
11	20A; 18S	4.7	142	104	23	6	45A; 33S	3.8	140	99	28	0.3–1.4
12	23A; 17S	4.3	143	103	24	6	62A; 28S	4.2	141	100	24	0.3–1.3

A = while awake; ECG = electrocardiogram; S = while asleep.

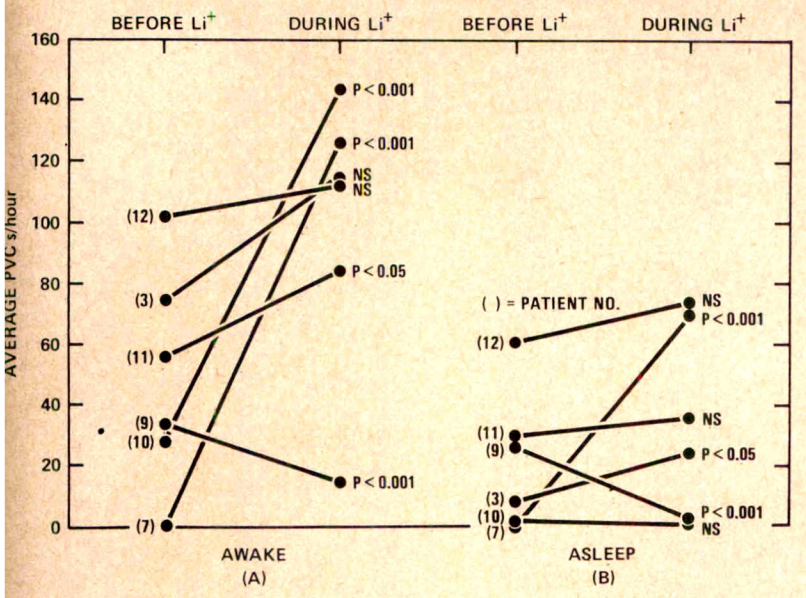


FIGURE 1. Effect of lithium on premature ventricular contractions (PVC's) during waking hours (**A**) and sleep (**B**). The level of statistical significance of the change in mean number of premature ventricular contractions per hour is given for each patient. During the waking state, the frequency of these contractions increased in three patients, lessened in one and showed no change in two. During sleep, the frequency increased in two patients, lessened in one and showed no change in three. NS = not significant; P = probability.

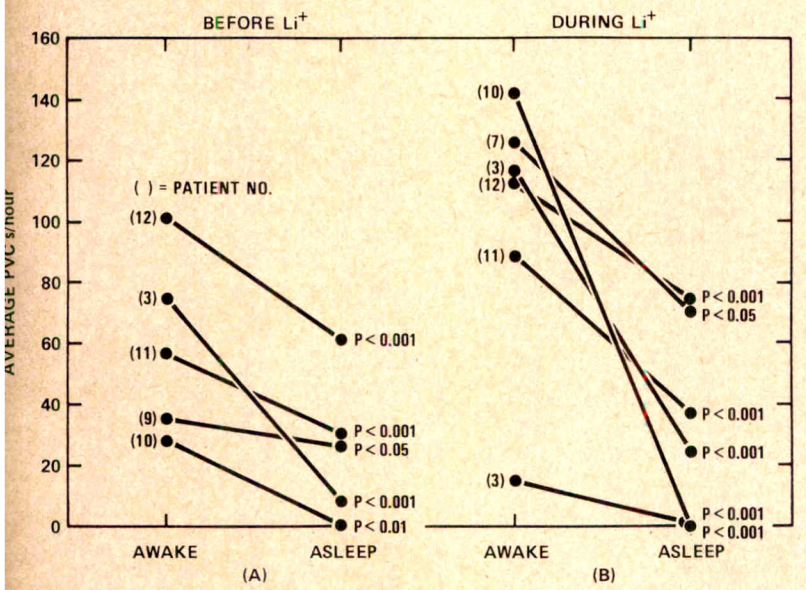


FIGURE 2. Effect of sleep on premature ventricular contractions in patients with more than 100 such contractions in 24 hours, before (**A**) and during (**B**) lithium therapy. The level of statistical significance of the change in mean number of premature ventricular contractions per hour is given for each patient. All patients showed a decrease in frequency during sleep both before and during lithium therapy.

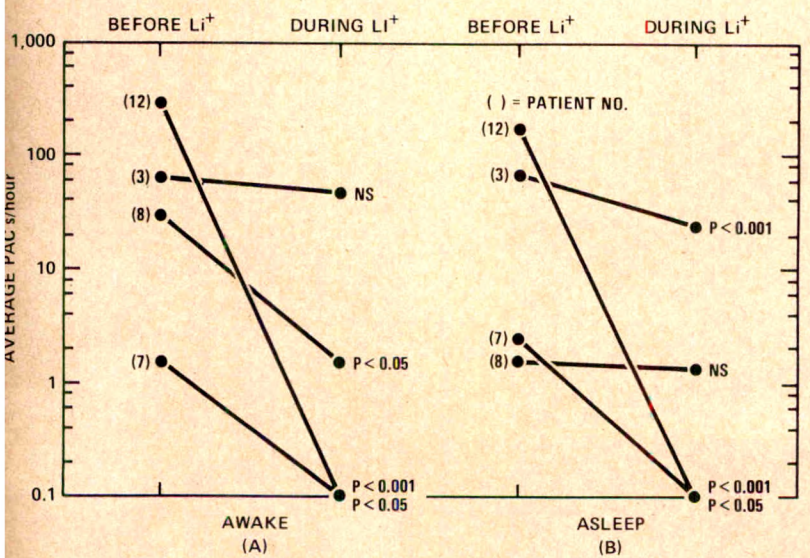


FIGURE 3. Effect of lithium on premature atrial contractions (PAC's) during waking hours (**A**) and sleep (**B**). The level of statistical significance of the change in the mean number of premature atrial contractions/hour is given for each patient. In three of our patients who had premature atrial contractions before lithium therapy the contractions decreased in frequency during both waking hours and sleep after lithium therapy. The effect of sleep on frequency was inconsistent.

tractions during the control monitoring period. While awake during lithium therapy, two patients had more frequent premature ventricular contractions, two showed no change and one had fewer premature ventricular contractions. Only one patient (Case 7) had frequent premature ventricular contractions during lithium therapy but none before therapy (Fig. 1A). The effect of lithium on these six patients during periods of sleep was similar (Fig. 1B).

Effect of sleep: Before lithium therapy, all patients with frequent premature ventricular contractions had a highly significant decrease in these arrhythmias during sleep. This apparent antiarrhythmic effect of sleep remained unchanged during lithium therapy (Fig. 2).

Complex ventricular arrhythmias: Episodes of multiform premature ventricular contractions, couplets, bigeminy or ventricular tachycardia were seen in four patients both before and during lithium therapy. It was not possible to count all such episodes accurately, but no clear increase after lithium was noted (Table III). Symptomatic arrhythmia did not develop in any patient.

Atrial Arrhythmias

Atrial arrhythmias were rare (Table III). Five patients (Cases 1, 5, 9, 10 and 11) had none, three (Cases 2, 4 and 6) had rare premature atrial contractions before lithium therapy, with no change during therapy. Four patients had a rate of 1.6 to 284.0 such contractions per hour before lithium therapy. Three of these four patients had a decrease in frequency of these contractions during lithium therapy, both while awake and while asleep (Fig. 3).

Supraventricular tachycardia of 5 to 10 beats was recorded seven times in two patients before—and once during—lithium therapy.

Table III provides a summary of all arrhythmias observed during ambulatory electrocardiographic monitoring. Three patients (Cases 7, 10 and 11) had more frequent or more severe ventricular arrhythmias during lithium therapy, one patient (Case 9) showed improvement and eight showed no change. In all patients with premature atrial contractions or supraventricular tachycardia, these arrhythmias decreased during lithium therapy, and neither arrhythmia developed during lithium therapy.

Exercise Electrocardiogram

Exercise performance: The results of the exercise electrocardiogram are summarized in Table IV. Duration of exercise before and during lithium therapy was identical for all 10 patients, indicating that no deterioration of exercise capacity occurred during therapy. At the same work load for the two exercise tests, the maximal heart rate before lithium therapy was slightly higher than that observed during therapy ($P < 0.05$).

Peak systolic blood pressure during exercise showed no significant change during lithium therapy. The heart rate times systolic blood pressure (double product) showed a small but significant decrease during lithium therapy ($P < 0.05$). This change reflected the lower heart rate during lithium therapy.

There were no ischemic S-T segment abnormalities during lithium therapy. Only one patient (Case 12), who had angiographically documented coronary artery disease and previous myocardial infarction, manifested 1 mm S-T depression before lithium therapy and this finding remained unchanged after lithium therapy.

Arrhythmias during exercise: Arrhythmias present during exercise and 8 minutes of recovery are summarized in Table V. Before lithium therapy, four patients had premature atrial contractions at a rate of 1 to 4/100 sinus beats. No patient had such contractions

TABLE III

Summary of Arrhythmias Observed During Ambulatory Electrocardiographic Monitoring in All Patients

	Before Lithium Therapy		During Lithium Therapy	
Case no.	Arrhythmia	Hours of ECG	Arrhythmia	Hours of ECG
1	NSR	46	Single PVC	44
2	5 PVCs	28	No PVCs, 1 PAC	16
3	Frequent multiform PVCs, bigeminy, couplets; frequent PACs, SVT (×5)	46	No change	17
4	PVCs, 1/hour, PACs, 1/hour	47	No change	43
5	NSR	37	No change	46
6	NSR	34	Single PVC, 7 PACs	34
7	PACs 1/hour, SVT (×2); no PVCs	27	No PACs, no SVT; frequent PVCs	38
8	Frequent PACs, PVCs, 1/hour	43	↓ PACs; no change PVCs; A-V dissociation (×7 hours)	41
9	Frequent multiform PVCs	74	↑ PVCs	100
10	Frequent uniform PVCs	42	↑ PVCs	193
11	Frequent multiform PVCs, couplets (×26), VT (3-4 beats) (×1)	38	↑ PVCs, couplets (×41), VT (×4)	78
12	Frequent multiform PVCs, couplet (×1); frequent, PACs	40	No change in PVCs, couplet (×1), ventricular bigeminy; no PACs	90
Total		502		740

↓ = decreased; ↑ = increased; A-V = atrioventricular; NSR = normal sinus rhythm; PACs = premature atrial contractions; PVCs = premature ventricular contractions; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

TABLE IV
Exercise Performance in 10 Patients Before and During Lithium Therapy

	Before Lithium Therapy (mean ± SD)	During Lithium Therapy (mean ± SD)	Statistical Significance
Duration of exercise (sec)	457 ± 168	459 ± 170	NS
Heart rate (beats/min)	153 ± 19	147 ± 19	$P < 0.05$
Systolic blood pressure (mm Hg)	169 ± 20	162 ± 19	NS
Heart rate-blood pressure product/100 beats	256 ± 39	238 ± 28	$P < 0.05$
Ischemic S-T depression (no. of patients)	1	1	NS

NS = not significant; P = probability; SD = standard deviation.

TABLE V
Exercise-Induced Arrhythmias Before and During Lithium Therapy

Case no.	Before Lithium Therapy		During Lithium Therapy	
	PACs*	PVCs*	PACs*	PVCs*
1	1	+	+	+
2‡	. . .	. . .	. . .	. . .
3‡	. . .	. . .	. . .	. . .
4	+	+	+	+
5	+	+	+	+
6	1	+	+	+
7	+	+	+	+
8	1	+	+	+
9	+	2 (unifocal), 1 couplet	+	+
10	+	15 (unifocal), VT (6 beats)	+	17 (unifocal), couplets
11	+	12 (unifocal), couplets	+	4 (multifocal, no couplets
12	4	2 (multifocal)	+	2 (multifocal)

*Reported per 100 sinus beats.
†No arrhythmia detected.
‡Patient refused exercise test.
PACs = premature atrial contractions; PVCs = premature ventricular contractions; VT = ventricular tachycardia.

on exercise during lithium therapy. There were no episodes of sustained supraventricular tachycardias during either test. Before lithium therapy, four patients had premature ventricular contractions during exercise, ranging from 2 to 15/100 sinus beats. Complex ventricular arrhythmias developing in these patients before lithium therapy included multifocal premature ventricular contractions, couplets and a short run of ventricular tachycardia. During lithium therapy, Patient 9 remained free of premature ventricular contractions, Patient 10 had an unchanged number of such contractions and manifested frequent couplets but no ventricular tachycardia. Patient 11 had a decreased frequency of premature ventricular contractions and no couplets; only Patient 12 showed no change. No patient free of ventricular arrhythmias during exercise before lithium therapy had such arrhythmias during lithium therapy.

Discussion

Lithium was introduced to psychiatric therapy by Cade[1] in 1949 but has achieved general acceptance and widespread use, particularly in the United States, only in the past 5 years.[2] The reasons for this slow acceptance in the United States were several: (1) reports of fatal lithium intoxication during its uncontrolled use as a salt substitute; (2) preoccupation with other psychopharmacologic agents that were simultaneously introduced; and (3) lack of interest on the part of pharmaceutical companies in a nonpatentable drug.[9]

Reported cardiac effects of lithium: At present, lithium is considered the treatment of choice for the *long-term* control of mania in manic-depressive psychoses and the prevention of relapse in bipolar manic-depressive illness. With the increasing use of lithium, various side effects and manifestations of toxic effects have been reported, including those involving the cardiovascular system. Recent reviews[2,6] have shown the cardiac effects of lithium to be variable. Lithium in dogs, in short-term preparations and large doses, has been reported to cause hypotension and cardiac arrest.[10,11] At a slower rate of intravenous administration, lithium is reported to have antiarrhythmic[12–14] and positive inotropic effects[15] in experimental models. We were unable to find any studies on the effects of long-term lithium administration on myocardial contractility in animals or man. Therapeutic doses of lithium in man cause reversible T wave changes.[16–18] Two single case reports have attributed premature ventricular contractions[19] and symptomatic sinus nodal dysfunction[20] to the use of lithium in therapeutic doses.

Cardiac abnormalities were seen rarely in patients during *lithium intoxication*, and serious arrhythmias have been reported in only three patients.[21–23] Fatal lithium intoxication always presents with severe abnormalities of the central nervous system. Pulse irregularities, hypotension and circulatory collapse, generally listed among the toxic cardiac effects of lithium, occurred only after prolonged coma.[24–28]

Lithium and ambulatory arrhythmias: Our ambulatory electrocardiographic monitoring data suggest that long-term lithium administration in man in *therapeutic doses* may induce (one of six patients) or aggravate (two of six patients) preexisting ventricular arrhythmias in the absence of other electrolyte abnormalities. In contrast, atrial arrhythmias, although few, seem to decrease during lithium therapy.

Lithium and exercise performance: Our results show that lithium in therapeutic doses in man does not adversely affect exercise performance. Time spent on the standardized treadmill is a reliable indirect measurement of maximal oxygen consumption and, in the absence of lung disease or anemia, closely reflects maximal cardiac output. Interventions that would decrease myocardial contractility and cardiac output would be expected to decrease the duration of maximal exercise.[29]

Resting heart rate was not affected by lithium therapy. There was a small but significant decrease in the heart rate-systolic blood pressure product (double product) during lithium therapy at the same level of exercise as before lithium administration. This change was due to the slower heart rate during exercise because changes in the systolic blood pressure were not different. This improvement in performance cannot be attributed directly to lithium because such changes can be secondary to a "learning effect" from the first to the second test.[30] Although hypotension and cardiovascular collapse are listed as cardiotoxic effects of lithium, these have been reported only after severe lithium intoxication and prolonged coma. Our findings indicate that in therapeutic doses lithium does not adversely affect maximal cardiac work.

Lithium and exercise-induced S-T changes: In six patients T wave depression developed in the resting electrocardiogram during lithium therapy, a finding similar to that reported previously.[16–18] The mechanism proposed for this effect is intramyocardial replacement of potassium ion with lithium. Potassium depletion[31] and digitalis,[32] which alter the intramyocardial ratio of potassium ion to sodium ion,[33] are known to cause false-positive ischemic S-T depression in the exercise electrocardiogram. Nine of 10 patients had no S-T depression on exercise, before or during lithium therapy, and the 1 mm depression noted in the patient with coronary artery disease did not change during lithium therapy. Thus, as detected by the stress electrocardiogram, lithium does not cause myocardial ischemia, exacerbate preexisting ischemic responses or cause a false positive response. This observation should prove valuable in the evaluation of suspected coronary disease in patients receiving lithium therapy.

Lithium and arrhythmias during exercise: Lithium therapy abolished premature atrial contractions during exercise in four patients. None of the other eight patients had atrial arrhythmias during exercise while receiving lithium. These findings are in agreement with the data obtained during ambulatory electrocardiographic monitoring and further strengthen the suggestion that lithium may be beneficial in controlling atrial tachyarrhythmias. In the three case reports of serious arrhythmias during lithium intoxication, the abnormalities included sinoatrial block, atrioventricular (A-V) block and A-V dissociation.[21–23]

Ventricular arrhythmias (premature ventricular contractions, couplets and ventricular tachycardia) during exercise and the immediate recovery period decreased in three of the four patients during lithium therapy. This finding is somewhat at variance with the ambulatory electrocardiographic monitoring data, which showed an increase in frequency of premature ventricular contractions during lithium therapy in 3 of 12 patients. Since these tests were performed in the same patients during the same study period, this difference probably reflects the different method of testing. The value of ambulatory electrocardiographic monitoring in arrhythmia detection has recently been compared with that of the exercise electrocardiogram.[34,35] Both methods were considered effective in detecting arrhythmias, but each may yield different information about the electrophysiologic state of the myocardium.[35] Arrhythmias detected with ambulatory electrocardiographic recording are probably better understood than are those provoked by exercise, with regard to their significance and associated risk.[36]

Therapeutic Implications

From our findings we conclude that in therapeutic doses (1) lithium does not adversely affect cardiac function, as measured by treadmill testing; (2) proposed lithium-related electrolyte shifts affect the T wave of the resting electrocardiogram but do not result in resting or exercise-induced S-T segment abnormalities; (3) lithium decreases the frequency of preexisting premature atrial contractions and may decrease the frequency of paroxysmal supraventricular tachyarrhythmias; and (4) lithium does not aggravate exercise-associated ventricular arrhythmias, but ambulatory electrocardiographic monitoring data suggest that ventricular arrhythmias may occur or be aggravated during lithium therapy.

The presence of heart failure, salt restriction[37] and long-term use of diuretic agents[38] all decrease the renal clearance of lithium, which could result in lithium toxicity. However, lithium can be used in cardiac patients if factors interfering with its excretion are identified and the dose adjusted accordingly. Until further studies provide more experience, patients with ventricular arrhythmias or sinus nodal dysfunction should be followed up closely with frequent electrocardiographic monitoring during lithium therapy.

Studies in long-term animal models and further investigation in man are necessary for better understanding of the cardiac effects of lithium therapy.

Acknowledgment

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Guest Editor

Introduction

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Fifty years ago, Blumgart and Yens[1] first used radioactive tracers in the detection and study of patients with heart disease. Their studies, representing the first applications of nuclear techniques to medical diagnosis, were performed almost 15 years before the first use of isotopes of iodine to study the thyroid.

Although tracers such as radioactive sodium and radioiodinated albumin were used in clinical research, the first procedure to achieve wide clinical use in cardiovascular nuclear medicine was the use of radioiodinated albumin to detect pericardial effusion, introduced in 1957 by Rejali et al.[2] in Cleveland. Lung scanning,[3] introduced in 1963, remains the most widely used procedure in cardiovascular nuclear medicine today although new procedures are rapidly reducing its predominance.

Nuclear techniques, in addition to their use in the care of seriously ill patients in coronary care units, are gradually achieving wide use in conjunction with exercise testing and in screening patients for congenital heart disease. Newer developments of simpler special purpose devices such as the nuclear "stethoscope" to provide left ventricular volume curves may some day bring certain aspects of cardiovascular nuclear medicine into the realm of office procedures.

The major role of cardiac diseases as a source of mortality and morbidity in industrialized countries, no less than the insidious onset of many of these diseases, has led to a whole series of technical advances aimed at diagnosing heart disease at the earliest possible stage. A major revolution in diagnostic accuracy occurred with the development of contrast angiography, which provides precise images of the structure and function of the heart including the coronary vessels.

The application of angiography is limited, however, by its complexity and occasional morbidity, since it does carry a slight risk of fatality (probably less than 0.1 percent). Although its exquisite visualization of the anatomy of the heart and the coronary vessels makes it an essential procedure in candidates for surgery, angiography can hardly meet the needs of the huge numbers of patients with suspected or proved coronary arterial lesions and other forms of heart disease. Nor is it acceptable as a means of frequently monitoring the patient's response to therapy, whether surgical or medical.

These gaps in existing diagnostic technology are beginning to be filled by two new and largely complementary procedures: echocardiography and cardiovascular nuclear medicine. The former has proved especially valuable in diagnosing cardiac valve disease; the latter has thus far found its main application in assessing ventricular function, both regional and total, and therefore in diagnosing various types of myocardial disease.

The structural detail obtainable through cardiovascular nuclear medicine is by no means in a class with that yielded by contrast angiography; both the quality and resolution of images are far inferior. But broadly speaking, where contrast angiography concentrates on structure, cardiovascular nuclear medicine focuses on function. It is able to show whether the right or left ventricle is enlarged and whether there is myocardial hypertrophy or thinning of the ventricular wall. It can

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indicate whether ventricular motion is normally active or hypoactive, either generally or regionally, the latter condition pointing to focal weakening of the myocardium. Regional myocardial blood flow as well as ventricular wall motion can be examined simply and safely. The regional blood flow studies, carried out during exercise testing in association with electrocardiography, are being increasingly used when coronary disease is suspected, particularly when the indications are still sufficiently ambiguous to make the decision to perform contrast angiography difficult. An example is that of an airline pilot with electrocardiographic abnormalities detected on a routine examination. Hitherto, performance of contrast angiography was the only way to ascertain definitely whether coronary disease was present and whether the man could continue to fly. It is possible that in time angiography can be avoided in such patients by using radioactive tracer studies during exercise to indicate the presence or absence of coronary disease. While not fully validated as yet, the initial results with such studies in many institutions have been very encouraging.

The papers in this Symposium have been selected in an effort to survey the use of radioactive tracers in the study of cardiovascular disease and the care of patients. Some of the procedures and devices are still highly experimental. Others are gradually achieving an important role in patient care. The articles are not meant to be all-inclusive. Important procedures such as the use of radioactive gases to study the heart and lungs have been omitted, not because they are of less value but because their use is less widespread than that of some of the other methods. The series should be considered in the nature of a progress report rather than a critical review. If the papers serve to acquaint cardiologists with some of the present areas of research and to stimulate their participation in this exciting field, they will have served their purpose.

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Radioactive Tracers in Congenital Heart Disease

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Radionuclide angiocardiography is a useful method in the evaluation of patients with congenital heart disease, safely and nontraumatically. Physiologic variables such as transit times, cardiac output, left ventricular ejection fraction, stroke volume, end-diastolic volume can be measured accurately with this technique. An important application of radionuclide angiocardiography in children with congenital heart disease is in the detection, localization and quantification (pulmonary to systemic flow ratio) of intracardiac shunts and shunts between the great vessels.

This technique has been found useful in the evaluation of the newborn infant with cyanosis, the patient with a cardiac murmur and the patient who has had cardiovascular surgery. Newer mobile gamma camera-computer systems permit the performance of radionuclide angiocardiography in severely ill premature and newborn infants and patients during the early postoperative period. Specially designed magnifying collimators and the development of ultrashort-lived radionuclides should result in an overall improvement in the diagnostic capabilities of this technique and in a further reduction in the radiation dose.

The most common method employed to assess the structure and function of the cardiovascular system in children is cardiac catheterization with fluoroscopy and single or biplane angiocardiography. This method provides accurate information and has been responsible for many advances in the diagnosis and treatment of congenital heart disease. However, cardiac catheterization is traumatic and carries a small but definite risk of morbidity or rarely, mortality to the patient. In addition, the level of radiation during fluoroscopy and angiography is relatively high, and patients are often subjected to multiple cardiac catheterizations. The contrast material used for angiography is hyperosmolar and of relatively large volume. It is injected under high pressures that may cause transient physiologic alterations or, less frequently, permanent tissue damage.

Radioactive tracers, on the other hand, can provide useful information about the cardiovascular system with much less risk and trauma. Although their exact role in clinical practice has to be determined, it is already clear that many advances have taken place since the early work of Blumgart and Yens[1] and Blumgart and Weiss[2] nearly half a century ago. The most important advances have occurred during the past decade. The development of practical gamma scintillation cameras,[3,4] with on-line computer systems and short-lived radionuclides is, in great part, responsible for the recent advances in the application of radioactive tracers in the evaluation of the cardiovascular system. There are now radionuclide techniques for measurement of transit times, cardiac output, left ventricular ejection fraction, stroke volume and end-diastolic

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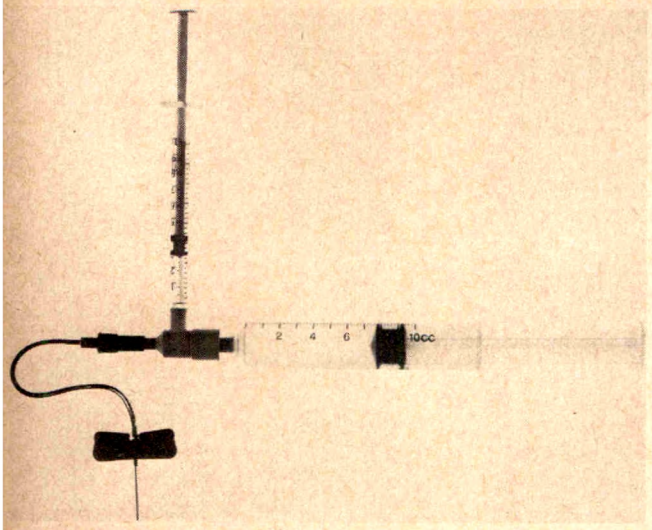


FIGURE 1. Radionuclide injector. A constant flow is initiated with the saline syringe, and the radionuclide solution is injected immediately to give a small and single bolus dose.

volume; detection, localization and quantitation of intracardiac shunts; measurement and imaging of myocardial blood flow; and detection, localization and sizing of myocardial infarcts. Radionuclide evaluation of congenital heart disease focuses on the use of radionuclide angiocardiography for evaluation and quantitation of shunts and for delineation of certain flow patterns (including pre- and postoperative evaluation).

Radionuclide angiocardiography[5] is defined as serial imaging of the passage of radioactive tracers through the cardiovascular system with a gamma scintillation camera. Data handling and analysis usually include the use of an on-line digital computer system.[6] Radionuclide angiocardiography is generally performed after administration of technetium-99m as sodium pertechnetate* or ^{99m}Tc human serum albumin. This technique requires a single intravenous injection, and is well tolerated even by severely ill children.[7,8] The volume of injectate is small, and there are no known or detectable hemodynamic or pharmacologic effects resulting from the administration of high specific activity radionuclide solution.

Radionuclide angiocardiography provides two kinds of information: *qualitative* (or morphologic) and *quantitative* (hemodynamic).[9] Anatomic information can be obtained with scintillation cameras and suitable recording equipment (videotape, cine film or timed scintiphotographs[10]) but such information is limited by the relatively poor resolution of current gamma cameras. Analysis of the information available in radionuclide angiocardiography is enhanced greatly by the use of on-line digital computer systems with which it is possible to record, store, display and analyze dynamic scintigraphic data.

On-line computer systems permit rapid and accurate processing of large amounts of data, a definite advantage when the information is to be used in decision making in the care of severely ill patients. Without modern computer systems, less information would be obtained with radionuclide angiocardiography and its clinical application would be limited. Although simple for the patient, radionuclide angiocardiography necessitates meticulous technique if reliable results are to be obtained and requires physiologic understanding if the maximal amount of information is to be derived.

Method

Patient preparation: Sodium perchlorate (intravenous) or potassium perchlorate (oral) is given in a dose of 6 mg/kg before radionuclide administration. In premature and newborn infants, sedation is not necessary; in a few children under age 8 years sedation may be required. Small patients must be immobilized; older children are more cooperative provided adequate explanations are given. A 23 or 25 gauge intravenous needle is inserted in the right external jugular vein and secured with tape (see later). The patient is then positioned with the gamma camera viewing the chest from the anterior (or left anterior oblique) position. Accurate positioning is achieved using radioactive markers over the suprasternal notch and xyphoid and ensuring that the chest is centered with the field of view of the gamma camera.

Radionuclide: Technetium-99m as sodium pertechnetate or ^{99m}Tc human serum albumin is given in a dose of 200 microcuries (μCi)/kg body weight. A minimal total dose of 2 to 3 mCi is necessary for reliable counting statistics. The radionuclide solution must be of high specific activity (30 to 40 mCi/ml) so that its volume is very small (0.1 to 0.5 ml). If more than one radionuclide injection is desired, it is possible to use high specific activity ^{99m}Tc(Sn) diethilenetriamine pentaacetic acid (DTPA)[8] complex, a chelate that is eliminated by glomerular filtration. Its use results in lower background levels for subsequent administrations of radionuclide.

Injection technique: The radionuclide is injected as a bolus dose and flushed with 1 to 10 ml of saline solution, depending on the patient's size. The bolus dose must be "unique," that is, nonfragmented, and have a duration of less than 2 seconds, as estimated from a time-activity curve generated from a small region of interest over the superior vena cava without pulmonary overlap. Delivery of such a bolus dose is important for clear temporal resolution and is required for accurate quantitative evaluation. If the dose has a prolonged duration or is fragmented, the study is considered inadequate for quantitative evaluations.[11,12] Injections in the right or left jugular vein result in a greater than 95 percent rate of satisfactory studies. Injections in the antecubital vein can be performed but result in a 15–20 percent rate of unsatisfactory studies (prolonged or fragmented bolus dose).

We designed a small disposable injector system* to allow injection of radionuclide solutions of small volume.[8] It consists of a one way valve injector connected to a scalp vein set with an inlet for a saline syringe and another for the radionuclide syringe. The injection is performed by initiating a flush of saline solution with one hand while holding the radionuclide syringe with the other. The radionuclide solution is then rapidly injected into the system without interrupting the saline flush (Fig. 1). A gamma scintillation camera views the passage of the radioactive bolus dose for approximately 30 seconds. The adequacy of the dose is evaluated in the computer while the patient is under the gamma camera.

* Technetium-99m has a physical half-life of 6 hours and decays with the emission of a monoenergetic 140 keV gamma ray.

* Paramedical Disposables Inc., Needham, Mass.

Data acquisition: Data are collected for 25 seconds in the computer,* which is on-line with the gamma camera† at 10 to 20 frames/sec on a 64 by 64 (byte) matrix for qualitative angiocardiography, shunt quantitation and calculation of ejection fraction. A collection period of 5 minutes at a rate of 1 frame/sec on the same matrix format is added for calculation of cardiac output. Images are usually displayed at a rate of 1 or 2 frames/sec for visual evaluation (Fig. 2). Calculations of the ratio of pulmonary to systemic flow (Qp:Qs) and cardiac output are performed with curves integrated to the rate of 2 frames/sec. Interpolating data on a finer matrix display (128 by 128 or 256 by 256) improves structural definition.

Data display and analysis: The first step in data analysis involves a visual evaluation on the computer oscilloscope of the series of images displayed at the rate of 2 frames/sec. Using an electronic "window" or "region of interest" mode, the operator selects areas over the cardiopulmonary structures from which time-activity curves can be generated. Since it is important to obtain curves without contamination from adjacent structures, it is helpful to subtract one phase of the study from another as an aid in selecting the regions of interest. For example, in the quantitation of left to right shunts, the frames corresponding to both the dextro- and levophases are subtracted from the frame of the pulmonary phase to be certain that only lung is being examined. Similarly, when trying to obtain curves from the right atrium and the right ventricle for localization of a shunt, it is important to avoid the levophase.

Qualitative analysis: This includes visual evaluation of the series of images and of the various time-activity curves as the tracer passes through the cardiopulmonary structures (superior vena cava, right atrium, right ventricle, lungs, left atrium, left ventricle and aorta). Occlusion of the superior (or inferior) vena cava or other abnormalities can be detected as interruption of the normal flow of radionuclide and the presence of collateral circulation. Gross poststenotic dilatation of the pulmonary artery and the aorta can also be detected with radionuclide angiocardiography. Pericardial effusion or large pericardial tumors appear as a nonperfused area in the series of scintigraphs. Right to left shunts are detected from the early appearance of radioindicator in the left side of the heart and the aorta before or at the same time as in the pulmonary circulation. The level of right to left shunts can be assessed by focusing attention on the cardiac chambers and the aorta. For example, in tricuspid atresia, Ebstein's anomaly, critical pulmonary stenosis and pulmonary atresia with intact ventricular septum, the tracer can be seen to flow through the right atrium and subsequently in the left atrium, left ventricle and the aorta. In right to left shunts at the ventricular level (tetralogy of Fallot, pulmonary atresia with ventricular septal defect, transposition of the great arteries with ventricular

* Gamma-11 (PDP 11/20) Digital Equipment Corporation, Maynard, Mass.

† Pho/Gamma HP—Searle Radiographics, Chicago, Ill. or Radicamera II, General Electric, Westwood, Mass.

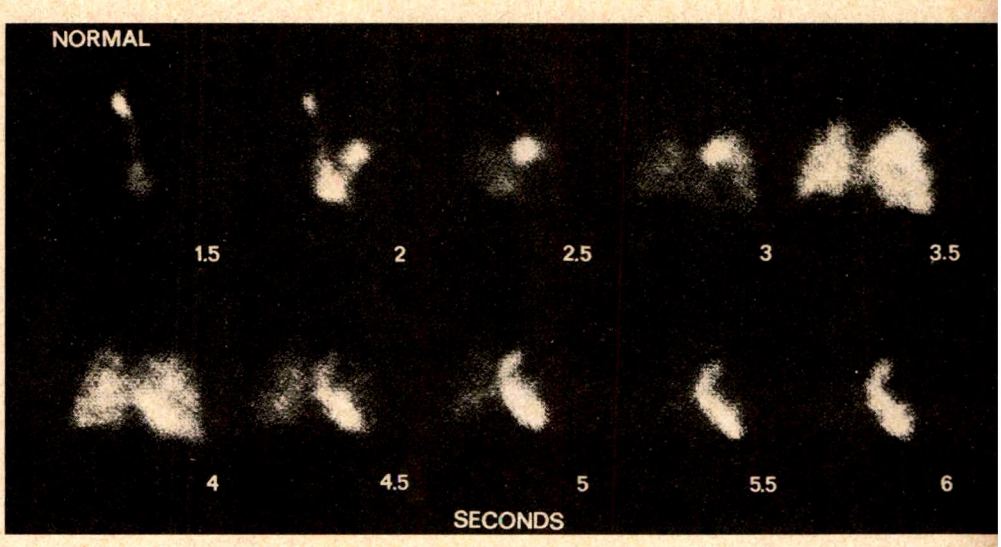


FIGURE 2. Normal radionuclide angiocardiogram. Anterior projection at 0.5 second intervals. The injection was performed in the right external jugular vein. The radioindicator is seen to circulate into the superior vena cava, right atrium (1.5 seconds), right ventricle, pulmonary artery (2 and 2.5 seconds), lungs (2.5 to 5 seconds), left atrium, left ventricle and aorta (3.5 to 6 seconds).

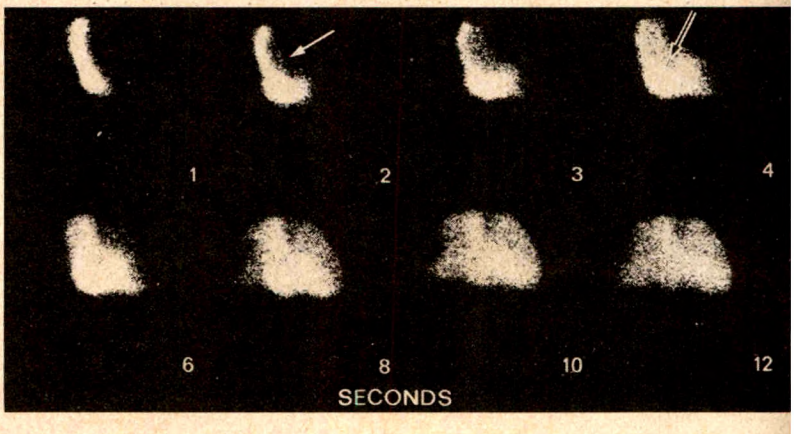


FIGURE 3. Right to left shunt at the ventricular level in a patient with tetralogy of Fallot and pulmonary atresia. Early appearance of radioactivity in the left ventricle and aorta (**white arrow**) is seen at 2 to 4 seconds. Ventricular shunting is confirmed at 4 to 6 seconds by the absence of radiotracer in the left atrium (central superior portion of the cardiac silhouette between the ventricles, **black arrow**), which fills with radioactivity after transit of the tracer through the lungs at 12 seconds. (Reproduced from Treves et al.[8] with permission of the W. B. Saunders Co.)

septal defect and Eisenmenger's syndrome), the radioindicator appears in the right ventricle, then the left ventricle and aorta. Only after the radionuclide has circulated through the lungs and only if it has not been greatly diluted can it be visualized in the left atrium (Fig. 3). In patent ductus arteriosus with right to left shunting, the tracer appears early in the aorta but not in the left ventricle.[8]

Left to right shunting can be diagnosed from simple observation of a series of scintigraphs.[10,11] Characteristically, there is persistence of high pulmonary levels of radioactivity with poor or no visualization of the left side of the heart and the aorta at the expected times (Fig. 4). However, very small left to right shunts cannot be detected in this way. Visual evaluation of pulmonary time-activity curves aids in this diagnosis. A normal pulmonary tracing (Fig. 5A) reveals no activity between the time of injection and appearance of the bolus dose within the lungs; a rapid upslope as the bolus dose enters the lungs; a peak as the maximal amount of activity is within the lungs; a nadir that does not reach the baseline; followed by another, less prominent, peak due to systemic

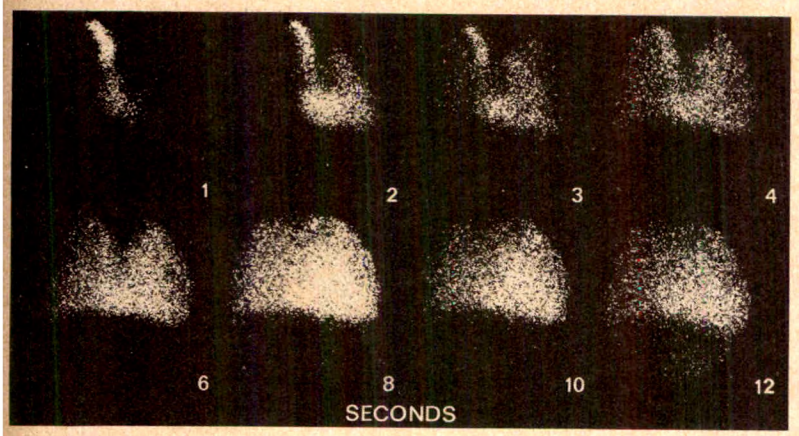


FIGURE 4. Left to right shunt in atrial septal defect. There is evidence of pulmonary recirculation with poor visualization of all structures after the first transit. Note the lack of visualization of the left heart and aorta. (Reproduced from Treves et al.[8] with permission of the WB Saunders Co.)

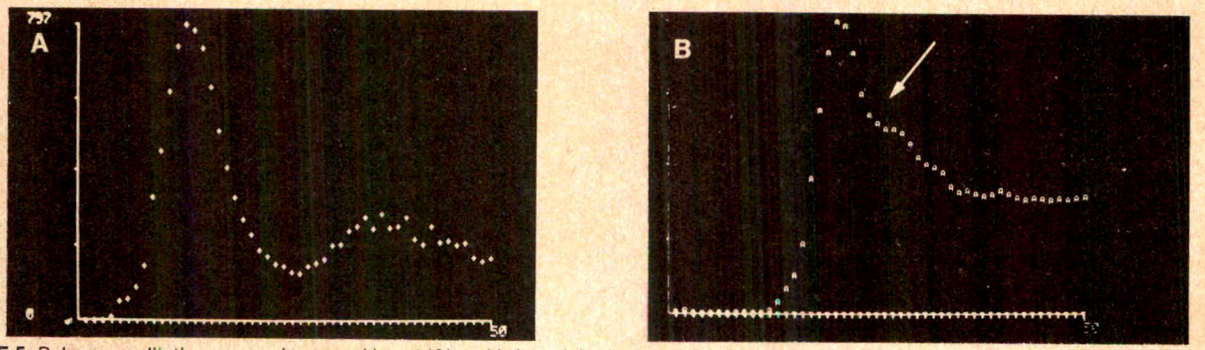


FIGURE 5. Pulmonary dilution curves in normal heart (**A**) and left to right shunting (**B**). The downslope after the peak is interrupted (arrow) by early pulmonary recirculation of radionuclide through the shunt.

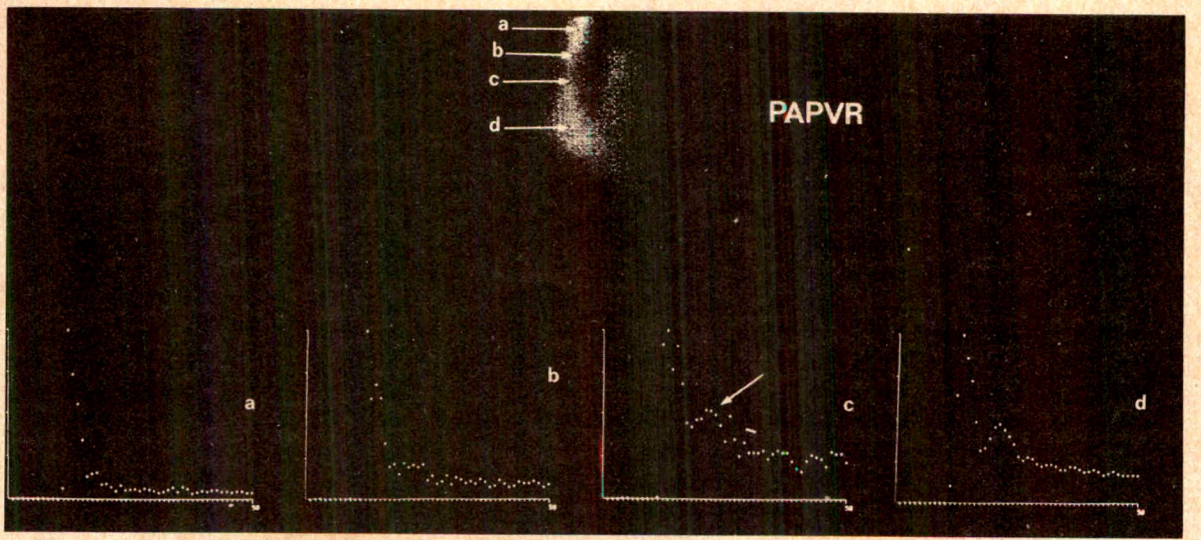


FIGURE 6. Time-activity curves in partial anomalous pulmonary venous return (PAPVR) to the superior vena cava. A second peak of early recirculation can be seen first on the superior vena caval curve (**arrow**), then in the right atrium (**d**).

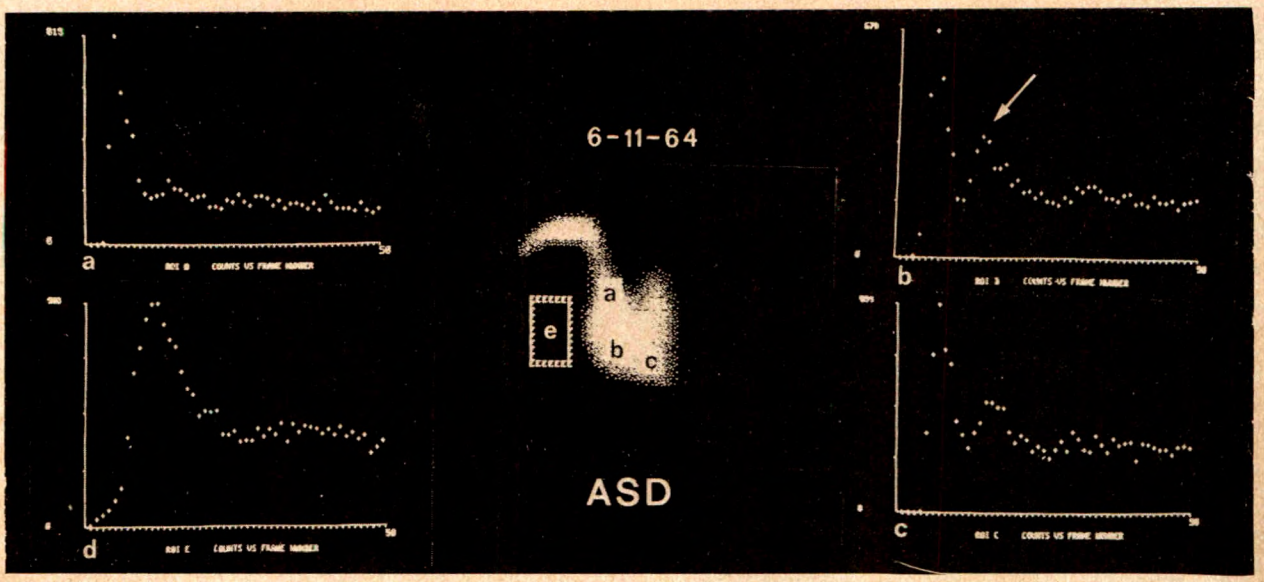


FIGURE 7. Time-activity curve in atrial septal defect (ASD). A second peak (left to right shunt) (**arrow**) is seen on the curve of the right atrium and ventricle (**c**). The pulmonary curve (**d**) also reveals early recirculation.

recirculation. In left to right shunting (Fig. 5B), the downslope following the first peak is interrupted by early pulmonary recirculation of radionuclide through the shunt. This is followed by series of small, gradually indistinguishable peaks due to subsequent systemic and shunt recirculations.[11–14]

A left-to-right shunt can be located by visually analyzing time-activity curves generated from the superior vena cava, right atrium, right ventricle and the lungs, thus defining the site of recirculation. Conditions for this are valve competence and the generation of "pure" curves (without contamination by radioactivity from adjacent structures). For example, in partial anomalous pulmonary venous return to the superior vena cava there is early recirculation in the superior vena cava, right atrium, right ventricle and lungs (Fig. 6), whereas in atrial septal defect (Fig. 7) there is early recirculation in the right atrium, ventricle and lungs. In ventricular septal defect there is early recirculation in the right ventricle and the lungs (Fig. 8). In patent ductus arteriosus there is early recirculation only in the lungs.[8,11,15,16] Dynamic scintigraphy in patients with patent ductus arteriosus reveals clear definition of the left side of the heart and aorta in spite of early pulmonary recirculation (Fig. 9). If more than one shunt is present, it is possible to localize only the most proximal.

Quantitative analysis: Quantification of left to right shunting is possible by numerical analysis of pulmonary time-activity curves. It has been shown that a gamma variate function well describes a single transit of indicator (without recirculation).[17–20] If only a segment of an indicator curve is available, the gamma variate can be used to construct a complete single transit curve. We recently reported a method that utilizes gamma variate fit to the pulmonary curves and provides pulmonary to systemic flow ratio (Qp:Qs).[11]

The gamma variate function is fit to the initial portion of the pulmonary transit curve, that is, from a point 5 to 10 percent of the peak activity on the upslope to a point when the downslope does not decrease uniformly (Fig. 10a). The area under this curve (A_1) is proportional to the pulmonary flood flow = Qp. If area A_1 is subtracted from the remainder of the pulmonary curve, another curve results (Fig. 10c), which represents the first early pulmonary recirculation due to the left to right shunt plus subsequent shunt and systemic recirculations.

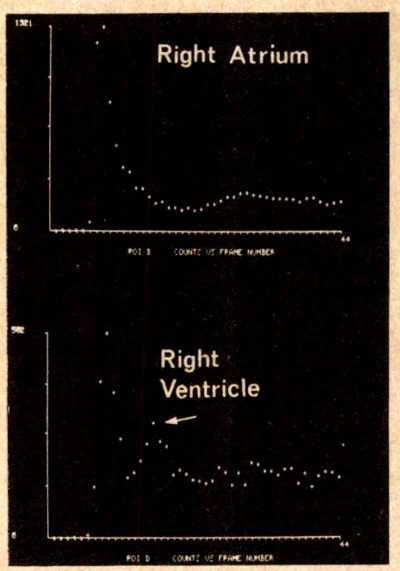


FIGURE 8. Time-activity curves in ventricular septal defect. **Top,** curve generated from a region over the right atrium; it appears monophasic. Bottom, curve from the right ventricle; it shows a second small peak (**arrow**) corresponding to early right ventricular recirculation due to left to right shunting.

A second gamma variate function is interpolated to the initial segment of the subtracted curve (Fig. 10) and another curve representing a single pulmonary transit is described. The area under this new curve (A_2) is proportional to the first early pulmonary recirculation due to the shunt (Fig. 10d). If the shunt flow area (A_2) is subtracted from the pulmonary flow area (A_1) the value that results represents the systemic flow ($A_1 - A_2 = Qs$). If now, A_1 is divided by $A_1 - A_2$, a pulmonary (Qp) to systemic flow (Qs) ratio results:

$$A_1/(A_1 - A_2) = Qp/Qs$$

This method can accurately quantify left to right shunts when the pulmonary to systemic flow ratio is between 1.2 and 3.0. Shunts greater than 3.0 generally produce pulmonary curves which are difficult to analyze. Comparison of this method with

cardiac catheterization (oximetry, left ventricular angiography and hydrogen studies) revealed a close correlation.[11] Analysis of the curve is done in the computer and requires close interaction of the observer to define segments of the curve to be "fit" and quality control of the "curve fits." When using the automatic computer algorithm in the fitting of the second or recirculation curve, we have occasionally recognized difficulties, usually in the form of second curve overfitting and consequent overestimation of the shunt (Fig. 10, g and h). We recommend definition of the curve segments by trained personnel or physicians for the first and second gamma variate fit as a solution to this problem. Clearly, fits as seen in Figure 10, bottom, are unacceptable and should not be used in shunt quantification.

Cardiac output can be calculated[21] from a time-activity curve obtained from the heart; a semilogarithmic extrapolation of the downslope of the left cardiac phase is used to determine the area under the curve (A). To correct for blood volume, it is necessary to collect information until the tracer (^{99m}Tc human serum albumin) reaches equilibrium (e) within the blood pool. Total blood volume (TBV) must then be determined independently. The formula for cardiac output (CO) is therefore as follows:

$$CO\ (ml/min) = (TBV \times e)/A$$

It is possible to calculate the amount of right to left shunting from intravenous injection of radiolabeled particles[22] such as ^{99m}Tc macroaggregates of human serum albumin or ^{99m}Tc microspheres of human serum albumin. Under normal conditions, most of these particles lodge in the pulmonary capillaries and only 3 percent go through the lungs. In right to left shunting, a variable percentage of these particles will

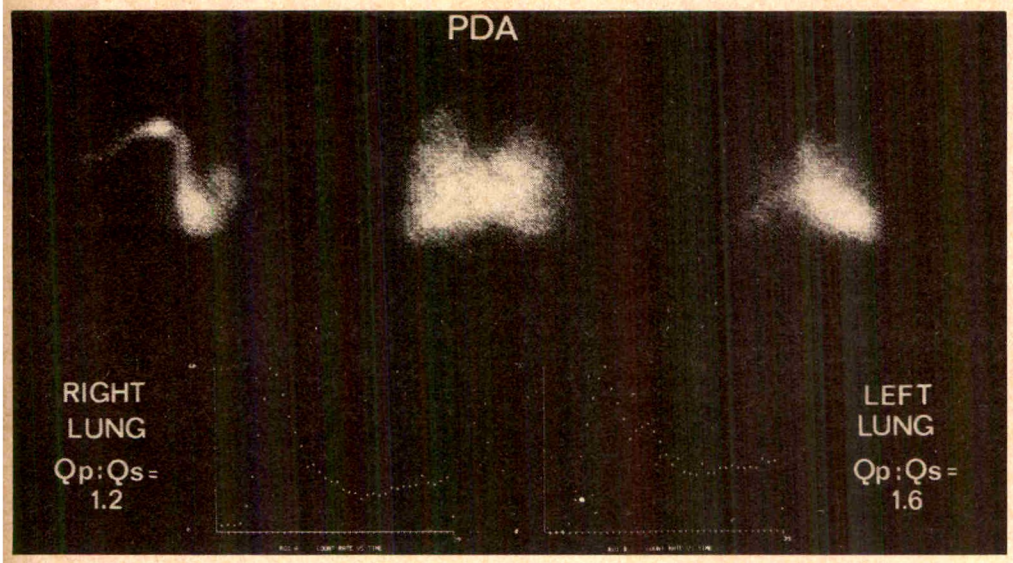


FIGURE 9. Patent ductus arteriosus (PDA). **Top left,** visualization of the superior vena cava, right atrium, right ventricle and pulmonary artery. Top center, visualization of part of the dextrophase and the pulmonary phase. **Top right,** clearly defined levophase and aorta in spite of pulmonary recirculation **Bottom,** time-activity curves from the right and the left lungs. Note the greater amount of early pulmonary recirculation in the left as compared with the right lung in patent ductus arteriosus. The estimated pulmonary to systemic flow ratio (Qp:Qs) is 1.6:1 in the left lung and 1.2:1 in the right lung.

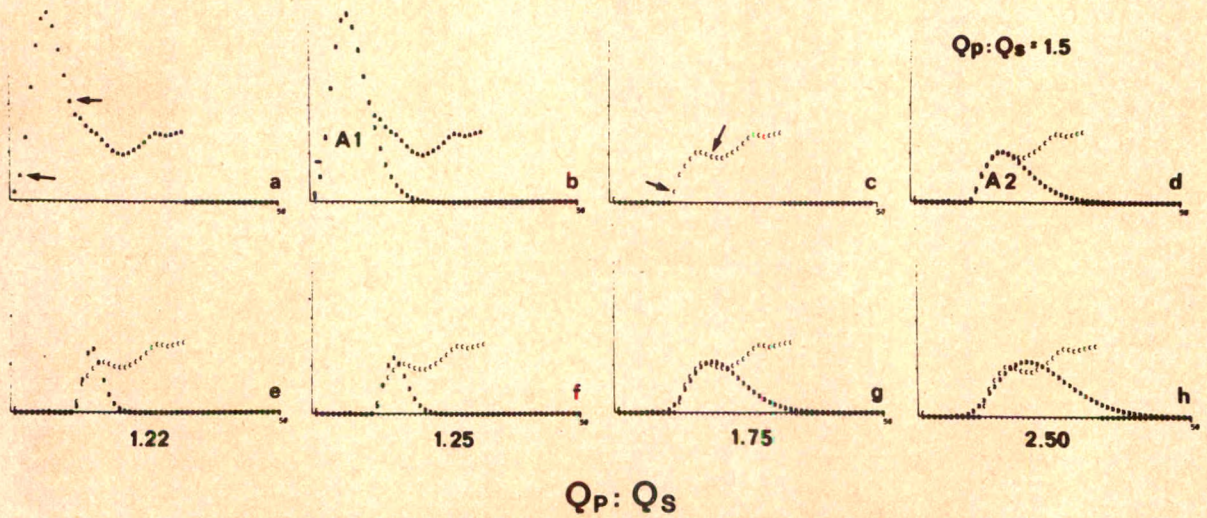


FIGURE 10. Calculation of pulmonary to systemic flow ratio (Qp:Qs) in left to right shunt. Gamma variate function fit is carried out over a segment of the pulmonary curve from a point about 5 to 10 percent of the peak on the upslope to a point on the downslope when decay is no longer monotonous (**arrows** in **a**) to define the first pulmonary transit, area A_1 (**b**). Area A_1 is subtracted from the remainder of the curve to obtain another curve representing the shunt and subsequent systemic and shunt transits (**c**). A segment of this curve is defined (**arrows** in **c**) and another gamma variate function is interpolated to define the first shunt flow area (area A_2 in **d**). The resulting ratio $A_1/(A_1 - A_2)$ = Qp:Qs. The segment defined includes the area from a point at 5 to 10 percent of the peak on the upslope to another point at or past the peak, if there is a small downslope. This part of the analysis is critical. It is necessary to obtain a close fit as seen in **d.** Second gamma variate fits, as seen in **e** and **f,** will cause underestimation of the shunt; fits as seen in **g** and **h** will cause overestimation of the shunt (the most frequent problem) and therefore must not be used for shunt calculations.

escape into the systemic circulation and lodge in the body organs with a distribution proportional to the regional partition of cardiac output. If the amount of radioactivity within the lungs (Qp) is determined and compared with that in the total body (Qs), a pulmonary to systemic flow ratio can be obtained (Qp:Qs). Although this method has been used in several institutions with safety, there is always the potential risk of accidental embolization of a systemic organ. Another method of quantifying right to left shunts analyzes activity curves generated from the right and left ventricles.[23] However, measurements of peripheral oxygen saturation made at cardiac catheterization are adequate for determining the functional size of right to left shunting, and radionuclide methods are not routinely used.

There are two major approaches to estimating left ventricular ejection fraction. One method uses ^{99m}Tc human serum albumin and electrocardiographically selected frames to portray end-diastolic and end-systolic images or multiple images throughout the cardiac cycle. This approach provides good spatial resolution and aids in detection of abnormalities of myocardial wall motion.[24] It can also serve to construct time-activity curves depicting changes in intracardiac volume. A second method relies on data obtained from the first transit of radionuclides through the left side of the heart.[25] With appropriately rapid frame rates (20 frames/sec), it is possible to define systole and diastole without electrocardiographic control (Fig. 11). Images for end-systole and end-diastole can be created by adding several systolic and diastolic frames during the first transit of indicator (Fig. 12), and the ejection fraction can be measured.

At present, radionuclide methods for measurements of cardiac output, right to left shunting and ejection fraction have not yet found a place in the evaluation of congenital heart disease, although this is likely to follow in the wake of their widespread application in patients with coronary heart disease.

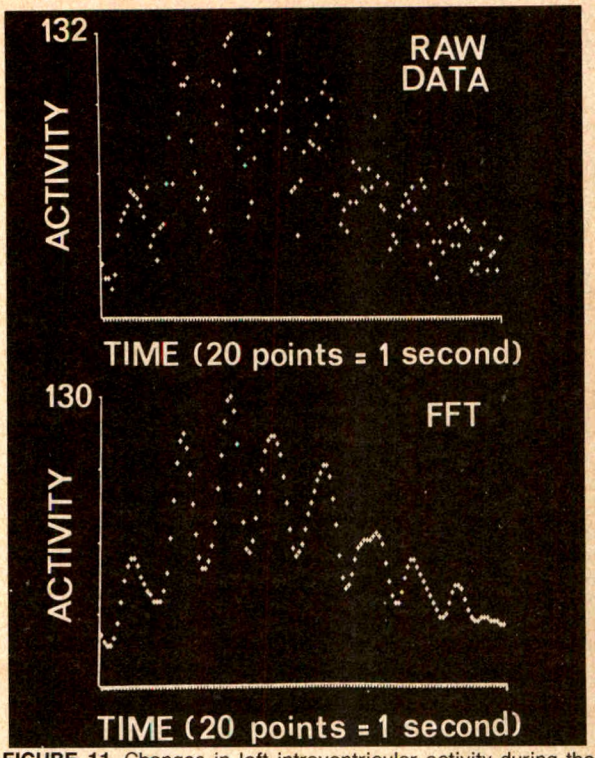


FIGURE 11. Changes in left intraventricular activity during the firs pass of radioindicator. **Top,** curve obtained from a region of interes over the left ventricle at a rate of 20 points per second during the firs transit of tracer in a normal subject. Note the oscillations correspondin to end-diastole and end-systole. With adequate definition of the le ventricular outline, it is possible to calculate ejection fraction for eac single heartbeat. **Bottom,** same curve after filtration of high frequenc data using a Fast Fourier Transform (FFT). Note how clearly defined th oscillations become.

Clinical Applications

Evaluation of the Newborn

Determining the origin of cyanosis in newborn infants is important in treatment. Radionuclide angiocardiography can aid in differentiating cardiac from pulmonary causes of cyanosis. In pulmonary disorders, the radionuclide angiocardiogram may appear normal although in cases of increased pulmonary vascular resistance it may show evidence of right to left shunting through a patent foramen ovale, a patent ductus arteriosus, or both.

Patent ductus arteriosus frequently coexists with prematurity and respiratory distress syndrome in the neonate and presents a complex problem in differentiating cardiac and pulmonary disease. To date, no quantitative methods are available to differentiate between pulmonary and cardiac factors contributing to the respiratory distress syndrome in these infants and no uniform guidelines have been established as to optimal time for surgical interruption of a patent ductus arteriosus, if present. The availability of portable gamma cameras has allowed quantitative measurement of the shunting through a patent ductus arteriosus and may prove useful in the pre- and postoperative evaluation and management of these infants. Newborn infants with cyanosis due to cardiac disease but without pulmonary disease can also be evaluated with radionuclide angiocardiography. For example, in transposition of the great arteries or a large right to left shun with severe pulmonary stenosis, the radionuclide ap pears promptly in the aorta before it appears in th lungs (Fig. 13).

Evaluation of the Patient With a Cardiac Murmur

In certain patients, it is difficult to determine th cause of a murmur. For example, in both atrial septa defect and pulmonary stenosis there may be wid splitting of the second heart sound with little respirator variation, and there may be a systolic ejection murmu Evidence of right ventricular hypertrophy in the elec trocardiogram and of pulmonary arterial enlargemer in the chest X-ray film may be present in both lesion The presence and magnitude of a left to right shunt ca be firmly established with radionuclide angiocard ography, thus allowing a clinical determination re garding the need for surgical closure of the defec without cardiac catheterization. In fact, estimation c shunt size with radionuclide angiocardiography may b more accurate in atrial septal defect than estimatio with oximetry since no true mixed venous sample available in patients with atrial septal defect.

The numerical data can also be used to differentiat between intracardiac and extracardiac shunts such a patent ductus arteriosus. In patent ductus arteriosus the distribution of blood flow in the pulmonar branches is asymmetric and usually favors the left lun

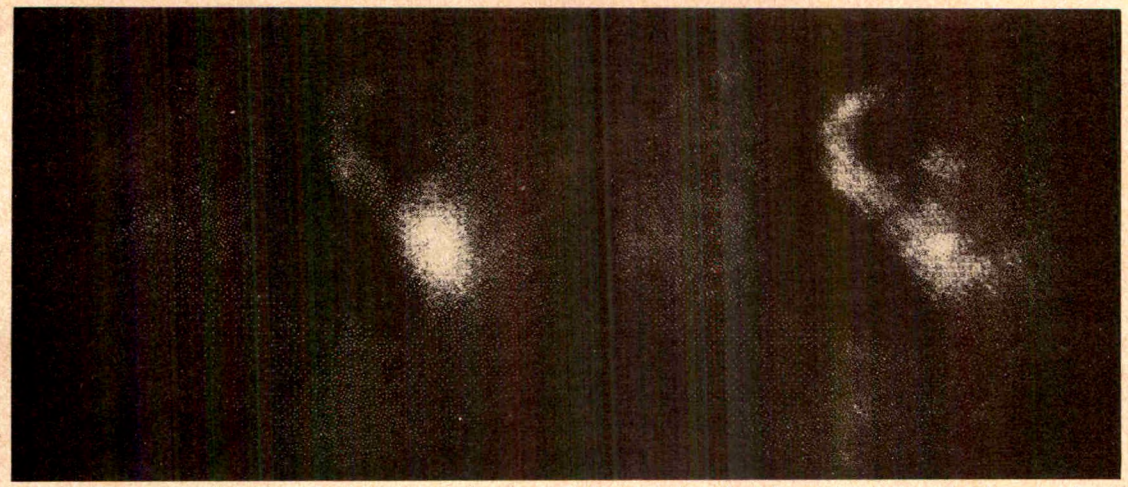


FIGURE 12. End-diastolic (**left**) and end-systolic (**right**) images in a normal 6 year old boy. Each image is composed of the sum of multiple points at end-diastole and end-systole during the first transit of radionuclide (see Fig. 11). The frames of the superior vena cava, right atrium and right ventricle were subtracted. Note the obvious difference between the end-systolic and end-diastolic outlines of the left ventricle and the apparent aortic "filling" during end-systole. With the aid of the computer, areas over the end-diastolic and end-systolic images can be constructed precisely and counted to calculate left ventricular ejection fraction = end-diastolic counts minus (end-systolic counts/end-diastolic counts).

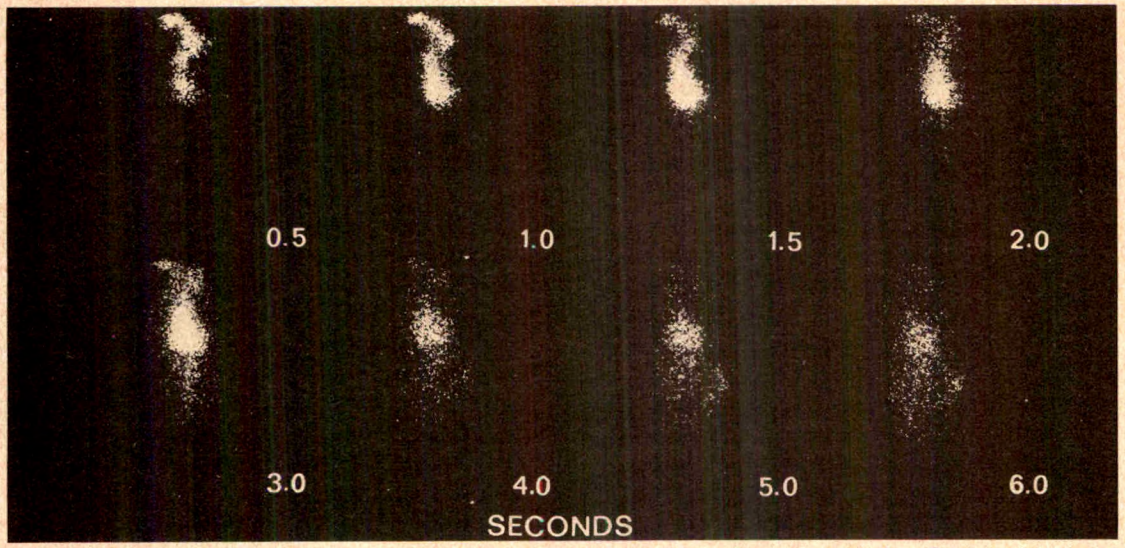


FIGURE 13. Transposition of the great arteries. Anterior radionuclide angiocardiogram obtained in a 4 day old infant. The bolus injection of radionuclide was given in the right jugular vein. The tracer is seen as it circulates through the superior vena cava into the right heart (0.5 and 1.0 second); the ascending aorta is visualized at 1.0 and 1.5 seconds and the descending aorta can be seen at 2.0 and 3.0 seconds. Note the very minimal or absent radioactivity within the lungs or in the left heart. (Reproduced from Treves et al.[8] with permission of WB Saunders Co.)

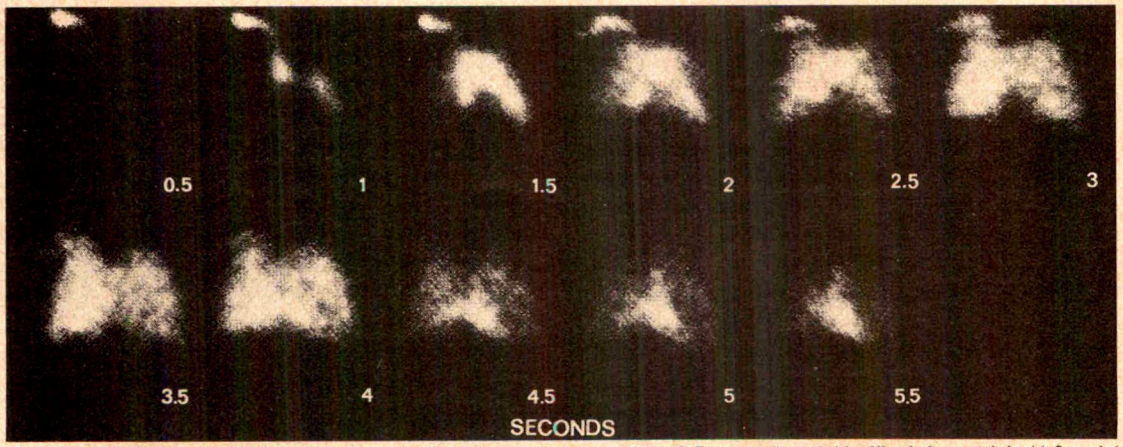


FIGURE 14. Mustard procedure. The radiotracer circulates in the superior vena cava (0.5 second), atrial baffle, left ventricle (1.0 and 1.5 seconds), pulmonary artery (2.0 and 2.5 seconds), lungs (2.0 to 4.5 seconds), common atrium (4.0 seconds), right ventricle and aorta (4.5 to 5.5 seconds). Note the absence of residual shunting or occlusion and the clear definition of the right ventricle and aorta.

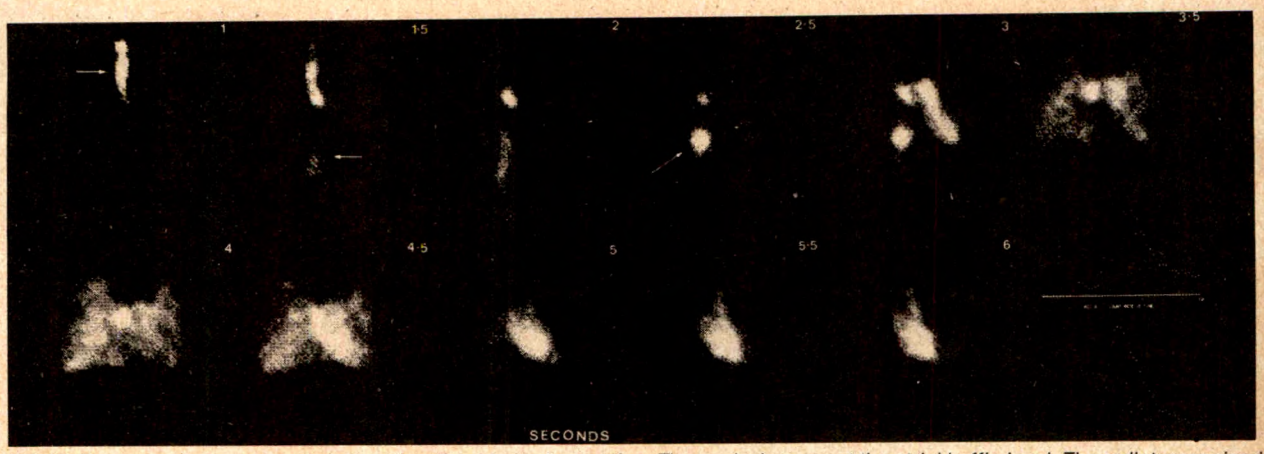


FIGURE 15. Total superior vena caval obstruction after Mustard operation. The occlusion was at the atrial baffle level. The radiotracer circulate in the superior vena cava (**arrow** at 1 second), but instead of going into the baffle and the left ventricle, it circulates well below the diaphragm t return by way of the inferior vena cava (**1.5 second arrow**), into the atrial baffle (**2.5 second arrow**), then into the left ventricle (3 seconds), pulmonar artery (3.5 seconds), lungs (3.5 to 4 seconds), common atrium, right ventricle and aorta (4.5 to 6 seconds). There is minimal or no residual shun ing.

A different pulmonary to systemic flow ratio should be calculated for each lung in these instances (Fig. 7).

Measurement of the size of the shunt is useful in managing of patients with ventricular septal defect. Although the type of murmur and the electrocardiographic and chest X-ray data may permit one to approximate the size of the shunt, radionuclide angiocardiography provides valuable quantitative information that contributes to clinical management. A small ventricular septal defect in the presence of normal pulmonary arterial pressures as assessed at cardiac catheterization may undergo spontaneous closure, and this fact can be documented with radionuclide angiocardiography. Preoperative cardiac catheterization is necessary to determine the number and location of the defects and to assess pulmonary arterial pressures in any patient with a large atrial or ventricular septal defect.

Evaluation of the Postoperative Patient

Persistent murmurs or the appearance of a new murmur postoperatively may imply residual lesions, detachment of the patch or valve abnormalities. In such cases, radionuclide angiocardiography allows rapid, safe and accurate detection and quantitation of any residual shunt. Reoperation can be carried out without prior cardiac catheterization if a large shunt is demonstrated with radionuclide angiocardiography.

Recently, total correction of transposition of the great arteries has been performed early in life with use of the Mustard operation. Radionuclide angiocardiography can assist in the early and late postoperative evaluation. A successful Mustard procedure provides a characteristic angiocardiographic pattern (Fig. 14). Complications of the Mustard procedure recognized with radionuclide angiocardiography include residual shunting through the atrial baffle, which can occur early or late in the postoperative period. Obstruction of the atrial baffle in either pulmonary or systemic circuits can be demonstrated rather dramatically with radionuclide angiocardiography (Fig. 15).

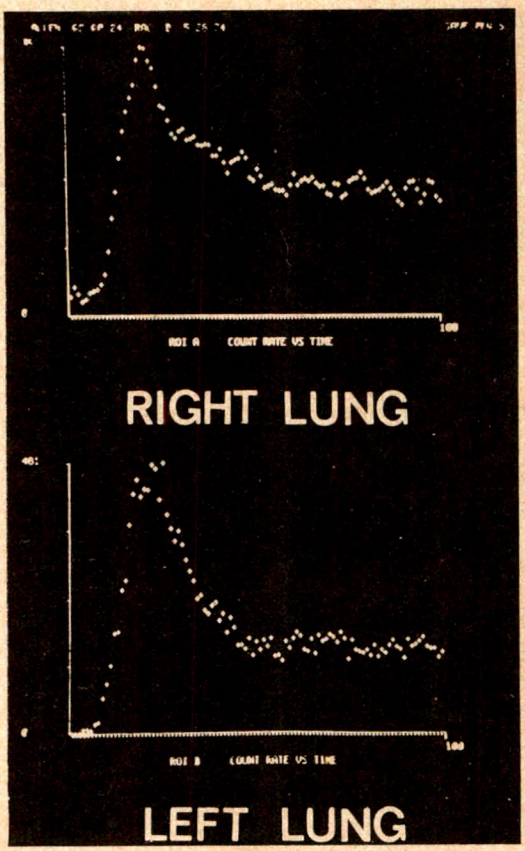


FIGURE 16. Pulmonary time-activity curves in Waterston anastomosi There is greater amount of early pulmonary recirculation in the rig than in the left lung because of the shunt.

Patency or occlusion of palliative shunts (Blalock Taussig, Potts, Waterston) can be demonstrated in vi sual evaluation of pulmonary dilution curves. The curv obtained over the lung on the side of the anastomosi reflects a larger early pulmonary recirculation than tha of the contralateral lung when the anastomosis is pater (Fig. 16).

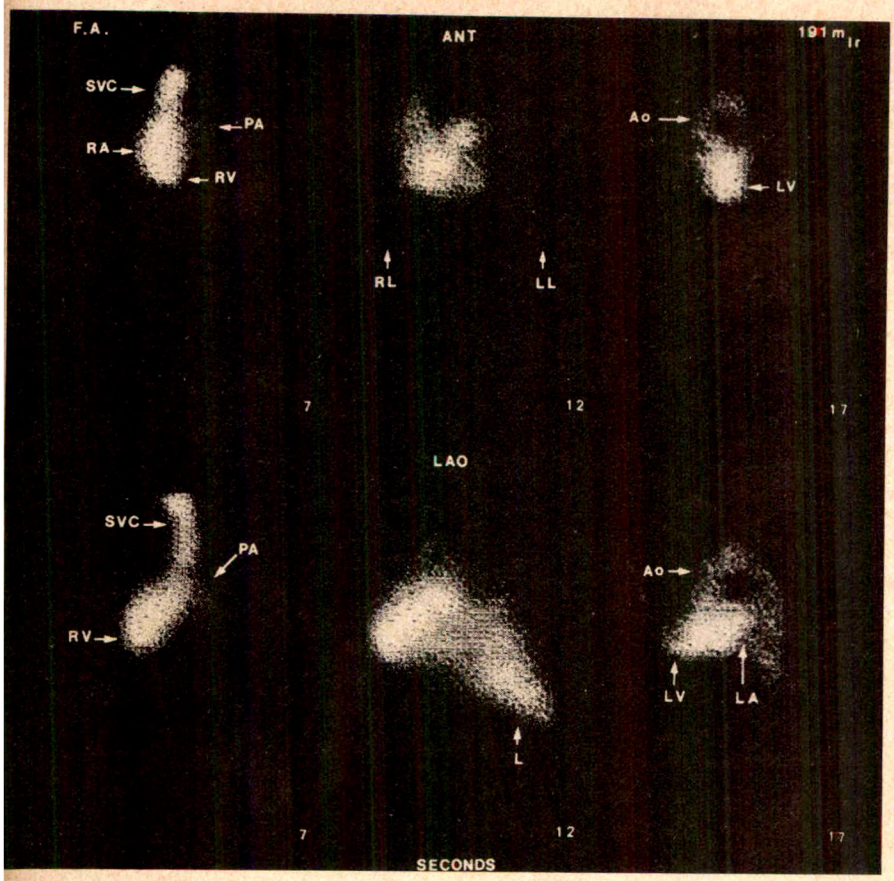


FIGURE 17. Iridium-191m (t 1/2 = 4.9 sec.) radionuclide angiocardiograms. Anterior (ANT) and left anterior oblique (LAO) projections obtained in a rhesus monkey. Eighteen mCi of ^{191m}Ir was delivered into a right antecubital vein. It is possible to follow the radiotracer through the superior vena cava (SVC), right atrium (RA), right ventricle (RV), pulmonary artery (PA), right (RL) and left (LL) lungs (L), left atrium (LA), left ventricle (LV) and aorta (A). These two projections were obtained within seconds of each other.

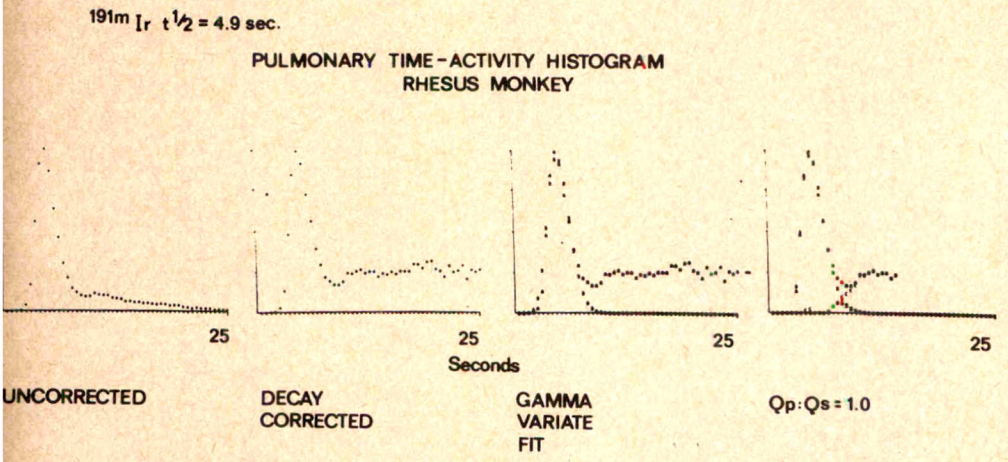


FIGURE 18. Iridium-191m pulmonary time-activity curve in a rhesus monkey. The uncorrected data are seen on the left. Note the rapid physical decay of the ^{191m}Ir. After correction for radioactive decay, a gamma variate fit was possible for estimation of pulmonary to systemic flow ratio (Qp:Qs), which in this case was 1.0.

Future Developments

Radionuclide angiocardiography is useful in evaluating patients with known or suspected congenital heart disease. It is relatively simple to perform, requiring only an intravenous injection of a radionuclide followed by serial imaging with a gamma camera. Both anatomic and quantitative physiologic data can be obtained. In selected instances radionuclide angiocardiography can be an alternative to cardiac catheterization. Its full diagnostic potential has not yet been reached. Of course, it does not provide the precise anatomic detail of conventional contrast angiography and cannot provide information on pressures or oxygen saturation data obtained during cardiac catheterization. Improvements in spatial resolution of imaging devices would certainly improve the quality of radionuclide angiocardiography. The development of magnifying collimators designed for premature and small infants would improve the overall spatial resolution of present gamma scintillation cameras, but these are not yet available. The converging collimators now available are inadequate for the study of small children.

An important use of radionuclide angiocardiography is in the evaluation of newborn infants and patients during the early postoperative period. Often these patients are too ill to be taken to nuclear medicine facilities

and consequently it is not generally possible to take advantage of the diagnostic potential of radionuclide angiocardiography. Newer mobile (portable) scintillation cameras permit the performance of radionuclide angiocardiography in these patients.

Another problem is the radionuclide used today in radionuclide angiocardiography. Although technetium-99m emits a gamma ray with an energy suitable for external detection with gamma cameras, its physical half-life is too long. This usually limits the study to a single injection and a single projection. If multiple projections and injections are necessary for diagnosis, the background radioactivity from the previous injection often results in images of poorer quality and distorted quantitative information. In addition, the patient continues to receive radiation for a longer period of time than is necessary for completion of the study (25 seconds). Ultrashort-lived radionuclides are a potential solution to these problems and, when readily available, should improve the quality of the diagnostic information from certain cardiovascular nuclear medicine studies. With such ultrashort-lived radionuclides, multiple projections could be obtained without undesirable background activity. In addition, the radiation exposure to the patient would be several hundred less than that of technetium-99m. We have been recently working with an osmium-191 → iridium-191m radionuclide generator.[26] Osmium-191 has a physical half-life of 15.3 days and decays to iridium-191m (half-life 4.9 seconds), which emits a 129 kiloelectron volt gamma ray. Although its physical half-life is extremely short, iridium-191m might be suitable for evaluating small children whose circulation time is rapid. Figure 17 shows two radionuclide angiocardiograms (anterior and left anterior oblique) obtained in a rhesus monkey after the intravenous injection of iridium-191m. With enough radioactivity and appropriate decay corrections, it is possible to handle time-activity curves derived from the heart and lungs (Fig. 18).

Looking at what has already been accomplished, we can only conclude that the future of radioactive tracers in the care of patients with congenital heart disease is bright indeed.

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Clinical Appraisal of Current Nuclear and Other Noninvasive Cardiac Diagnostic Techniques

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At a time of rapid increases in the cost of medical care and the application of complex invasive procedures to cardiovascular diagnosis, the use of noninvasive methods has aroused interest. This report discusses the usefulness and limitations of various noninvasive diagnostic methods including nuclear medicine techniques, echocardiography, exercise electrocardiography and determination of systolic time intervals. Emphasis is placed on the applicability of these methods to specific disease processes (such as ischemic heart disease, cardiac valve disease, pulmonary embolic disease), their relative merits, future potential and present shortcomings.

During the past decade, a variety of noninvasive cardiac diagnostic techniques have been introduced and are receiving increasing attention and acceptance. Interest in these procedures has been aroused by their ease of application, ability to provide meaningful results, repeatability, relative lack of expense and high degree of patient safety.

At a time of geometrically escalating costs of medical care and increasing awareness of the limitations of our resources, it is particularly important to have available noninvasive low risk inexpensive testing procedures for selecting patients who require or will significantly benefit from more costly invasive diagnostic and therapeutic procedures. If noninvasive techniques can provide adequate objective evidence that a person has no or only minimal cardiac disease, the savings realized through avoidance of further hospitalization for invasive diagnostic studies and absence from work would be considerable.

Noninvasive tests also have appeal to the referring physician provided he can feel assured that such procedures will yield important diagnoses with virtually no risk to the patient. Consequently, in applying these noninvasive procedures, we must carefully consider their usefulness in patient care as well as their inherent sensitivity and specificity as diagnostic tests. Unless the physician is aware of the diagnostic accuracy of each noninvasive test, he cannot justify the use of such testing simply because it is noninvasive. At times, a well chosen invasive investigation, even at some risk, may be preferable to a noninvasive "fishing expedition."

We have tried to highlight the developments in noninvasive diagnostic techniques over the past decade, emphasizing particularly their application to major problems in clinical cardiology. We have stressed the current usefulness and limitations of such procedures and their potential for solving problems in cardiovascular disease. Finally, we fully appreciate the clinical importance of older techniques such as the resting electrocardiogram and chest X-ray film. The value of these procedures to cardiovascular diagnosis has clearly been established and need not be considered here.

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Ischemic Heart Disease

Myocardial Infarction

A striking development in the past several years has been the ability to delineate acutely infarcted myocardium with radioactive tracers. Utilizing technetium-99m stannous pyrophosphate, Bonte and Parkey et al.[1,2] have shown a high correlation between acute myocardial infarction confirmed by electrocardiographic changes and serum enzyme studies and the appearance of a radioisotopic "hot spot" within the involved region 3 to 5 days after the acute event. McLaughlin et al.[3] found similar positive results up to 20 days after acute transmural infarction. With ^{99m}Tc tetracycline, Holman et al.[4] showed an excellent correlation of abnormal and normal myocardial scans with the presence or absence of documented myocardial infarction. They found peak activity within the heart 1 to 3 days after the clinical onset of chest pain. The scintigraphic site of the infarct correlated grossly with maximal serum creatine phosphokinase (CPK) activity in 16 patients. The method appears to be valuable for the recognition of acute myocardial infarction although more experience is needed to reach a consensus as to its sensitivity and specificity.

Diagnostic value: To the clinical cardiologist, the majority of patients presenting with acute myocardial infarction do not represent a diagnostic problem. Thus, the routine application of nuclear imaging of the zone of infarcted myocardium is not necessary for the proper care of most patients with this condition. However, this technique may be extremely helpful in certain circumstances. For example, the incidence of myocardial infarction after coronary bypass surgery has been reported to range between 5 and 40 percent.[5] Under these circumstances, the development of a diagnostic "hot spot" may allow more objective assessment of myocardial damage in a setting in which electrocardiographic S-T and T wave changes and routine serum enzyme levels can yield confusing results.[6,7] This technique should also prove helpful in diagnosing recurrent acute infarction in patients with preexisting Q wave abnormalities. Similarly, the test may be helpful in patients who are comatose or confused (due to trauma or alcoholism for example), and have nonspecific electrocardiographic and enzyme abnormalities for reasons other than acute infarction.

Assessing infarct size: An exciting aspect of the ability to radiolabel the infarcted myocardium is the concept that this method is qualitatively different from the traditional approaches of recognizing myocardial infarction in the living patient. Because in-hospital survival of the majority of patients with acute myocardial infarction appears to relate to the amount of damaged myocardium,[8,9] radiolabeling potentially affords the opportunity to derive quantitative assessment of the amount of injured tissue. This could provide an additional approach to the problem of infarct sizing, which is currently under intense investigation with other noninvasive studies such as serial CPK determinations and precordial S-T segment elevation mapping.[10–12] Whether this approach will yield additional meaningful information in a quantitative sense will be the subject of intensive clinical study over the next few years, in view of the current interest in therapeutic procedures that may modify the extent of damage to the acutely infarcted myocardium.

Diagnosis of Coronary Artery Disease

Assessing atypical chest pain: Considerably more troublesome than recognizing acute myocardial infarction is the problem of diagnosing coronary artery disease in patients with recurrent chest pain. The specificity of the syndrome of "classic" angina pectoris leaves little room for improvement with noninvasive diagnostic tests.[13,14] Nevertheless, many patients have recurrent chest pain with one or more atypical features[13]; in this group it is often difficult to establish an objective diagnosis of ischemic heart disease without performing coronary arteriography.

Electrocardiographic exercise testing: During the past 5 years, there has been renewed interest in exercise tests, particularly tests using graded protocols on a bicycle or treadmill to diagnose ischemic heart disease. The diagnosis is based on the appearance of 1 mm or more of horizontal or downsloping ("ischemic") S-T segment depression during or immediately after exercise.[15] The method has been clearly helpful in separating patient populations with and without significant coronary artery disease, particularly in view of long term prognosis, but its ability to indicate the presence of coronary disease in an individual patient has been less striking.[16] It has long been recognized[17] that as the degree of S-T segment depression increases to 2 or more mm, the test becomes considerably more specific but simultaneously less sensitive. Several reports[16,18–24] correlating the results of exercise testing with coronary angiographic studies have yielded widely variable sensitivity and specificity levels for the procedure. The disparities appear to stem in part from the nature of the groups studied. Thus, in asymptomatic patients selected for angiography on the basis of a positive exercise test there is considerably less specificity than in patients with classic angina who are studied similarly.[16,20] False positive tests often lead to coronary angiography. Properly executed, the risk of coronary arteriography is minimal and considerably outweighed by the reassuring evidence of a normal coronary circulation. More disturbing are independent reports of false negative electrocardiographic exercise tests in more than one half to two thirds of patients with arteriographically significant coronary lesions.[16,24] As a consequence, some investigators[16] have seriously questioned the diagnostic application of exercise testing to the clinical problem of ischemic heart disease. Certainly the procedure of exercise testing in search of ischemic S-T segment depression is an imperfect method for examining a large number of patients, particularly in view of the wide prevalence of coronary artery disease.

Myocardial perfusion imaging during exercise testing: It is in this context that recent studies by Zaret et al.[25,26] using the isotope potassium-43 have attracted

reat interest. By injecting this tracer during exercise nto patients with angina pectoris, they have shown the ack of uptake of the tracer in areas of the heart supplied y severely obstructed coronary arteries. These initial tudies raised the possibility of localizing ischemic areas f myocardium on the basis of failure of uptake of a adiolabel in involved muscle. The method has great ppeal because of its potential ability to quantify isch- mic areas of myocardium.

Because of its energy characteristics, potassium-43 s not an ideal tracer for such studies. For this reason, ome groups[27] have been unable to confirm the original bservations of Zaret et al. in localizing ischemic zones ith this method. More recent experience in several nstitutions, using thallium-201, has confirmed and xtended the usefulness of this method. It now seems kely that myocardial perfusion imaging will prove to e an alternative or supplemental method of measuring -T segment shifts. Despite its limitations, particularly ith S-T segment depression of 1 mm, exercise elec- rocardiography currently appears to be the most ractical available noninvasive means of objectively onfirming the presence of ischemic heart disease. In he face of a history of "classic" angina pectoris, how- ver, a negative exercise test must be regarded with onsiderable skepticism, and a thallium-201 study ould seem indicated.

The presence of coronary artery disease can also be nferred from detection of localized abnormalities of ontraction. Such abnormally contracting segments are ost prevalent in the distribution of significant coro- ary arterial lesions.

Assessment of Ventricular Function

In the past 5 years, several noninvasive techniques ave been advocated to reflect left ventricular perfor- nance. These techniques include determination of ystolic time intervals, echocardiography and imaging f the systolic and diastolic left ventricular chamber ith radioactive tracers.

Systolic time intervals: The determination of sys- olic time intervals is a completely noninvasive proce- ure and rapid and simple to perform.[28–30] However, the echnique is not widely used to assess ventricular unction. In part, this is a result of the extensive eval- ations of the technique in the setting of acute myo- ardial infarction.[31–33] In this situation, the hemody- amic variables upon which the values of preejection eriod and left ventricular ejection time depend are ften rapidly and acutely changing in opposite direc- ions so that changes in the intervals are not useful in ndividual patients. In addition, since the study of arrard et al.[34] there has been little confirmation of the iagnostic accuracy of systolic time intervals in pre- icting ventricular function in homogeneous patient roups. The technique is also further limited by its de- endence on the presence of normal intraventricular onduction and sinus rhythm.[35]

Echocardiography: Measurements made with this echnique have been shown to correlate with ventricular olumes and ejection fraction determined by invasive tudies.[36–38] However, the wisdom of predicting ven- tricular function in individual patients on the basis of transverse dimensional measurement of the left ven- tricle has been criticized.[39] The difficulties are partic- ularly evident in coronary artery disease wherein lo- calized disorders of left ventricular contractility can alter chamber dimensions in either direction depending on whether a hypocontractile or hypercontractile area of the ventricle is traversed by the echocardiographic beam. Nevertheless, the echocardiographic approach appears to have considerable potential for rapid non- invasive overall assessment of left ventricular function. The results of recent studies of Teichholz et al.[40] accu- rately predicting ejection fraction using the B scan technique support this contention. With the develop- ment of multiscan and sector scan approaches to the left ventricle, echocardiography may eventually prove to be the most practical and quickest means of assessing left ventricular function.[41,42]

Ventricular nuclear imaging: Utilizing the gamma camera and electrocardiographic gating, radionuclide evaluation of left ventricular function currently appears to be the best noninvasive means of approximating angiographic evaluation of left ventricular performance. Because the radioactive tracer technique can yield multiprojection planar images of the left ventricle throughout the cardiac cycle, this approach appears to be theoretically sound. Several independent studies[43–45] have shown correlation coefficients of 0.9 or better for ejection fractions obtained with nuclear imaging and angiography. Thus the radionuclide technique appears to offer 80 to 90 percent accuracy in predicting left ventricular ejection fraction.

The imaging achieved with nuclear techniques cannot be compared with the resolution obtainable with an- giocardiographic evaluation of the left ventricle. In particular, the margins of the left ventricular cavity and areas of transition between poorly and normally functioning segments of ventricular myocardium are poorly resolved. To those versed in the traditional angiographic evaluation of left ventricular performance, a procedure required by most surgeons today, radionuclide evalua- tion of left ventricular contractility is suboptimal. However, such evaluation appears able to distinguish patients with grossly poor ventricular function (ejection fraction less than 30 percent) from those with fair or good overall ventricular function. In this regard the radionuclide approach should receive greater attention. There is general agreement that preoperative assess- ment of left ventricular performance provides a mean- ingful index of the likelihood of survival after coronary bypass surgery.[5,46–48] In view of the increasing readiness to perform coronary angiography and bypass surgery to relieve angina pectoris, it may be worthwhile to use the nuclear approach for initial evaluation of ventricular performance. In those with definitely poor ventricular function, it would be reasonable to defer consideration of angiography and surgery until the results of intensive medical therapy are known.

Radionuclide imaging of the left ventricle also makes possible evaluation of segmental left ventricular dys- function. Detection of abnormally contracting segments can provide an important clue to the presence of coro-

nary artery disease.[49] Because the resolution of image is not ideal, the method is probably less sensitive for this purpose than for evaluating overall ventricular function. However, it appears to be the best noninvasive means of recognizing ventricular aneurysms, to which more conventional techniques are relatively insensitive.[50]

Cardiac Valve Disease

The clinical recognition of cardiac valve disease is less difficult than the recognition of coronary artery disease because physical examination usually gives important clues to the lesions present. In this condition, nuclear techniques have been less helpful than echocardiography or phonocardiography and pulse recordings for producing objective evidence of the presence and severity of a specific valve disorder.

Echocardiography

Hypertrophic subaortic stenosis: Echocardiography has been particularly useful in the recognition of the obstructive form of idiopathic hypertrophic subaortic stenosis, for which the systolic anterior motion of the anterior mitral leaflet apposing a hypertrophied ventricular septum is considered pathognomonic.[51–53] The proximity of the anterior mitral leaflet to the interventricular septum at the onset of systole also distinguishes most patients with the obstructive from those with the nonobstructive form of the disease.[54] Echocardiography has allowed a further appreciation of the spectrum of this disease since it has been shown that many relatives of patients with the obstructive form have asymmetric septal hypertrophy.[55] In fact, asymmetric septal hypertrophy appears to be the fundamental pathologic abnormality in both obstructive and nonobstructive forms of the disease.[56,57] More important, this lesion, which can be confused with mitral regurgitation, ventricular septal defect or even aortic stenosis, can objectively be defined without the need of cardiac catheterization. In many centers cardiac catheterization is no longer routinely performed in patients when this diagnosis can be confirmed by echocardiographic findings.

Mitral stenosis: The presence of mitral stenosis can usually be objectively confirmed echocardiographically with a specificity that approaches 100 percent. Although parallel anterior diastolic motion of the anterior and posterior leaflets of the mitral valve is not present in every case of mitral stenosis, considerably more than 90 percent of patients have this finding.[58–60]

Although the presence of mitral stenosis is confirmed relatively easily with echocardiography, its severity is somewhat difficult to determine by the single beam technique. There have been no published prospective series evaluating the accuracy of M mode scans in grading the severity of mitral stenosis. There is considerable variability of the E-F slope and other indicators of anterior leaflet motion in relation to severity.[61] With the single beam technique, it has been reported recently that leaflet separation correlated with mitral valve area with a correlation coefficient of 0.81.[62] Although this measurement was superior to the E-F slope, the method still accounts for only 66 percent of the variability of mitral valve stenosis in the group studied.

Using a sector scanner in the transverse position, Henry et al.[63] have shown that it is possible to visualize directly the mitral valve orifice. This approach appears to offer great promise as a sensitive noninvasive way of predicting accurately the severity of mitral stenosis.

Aortic stenosis: Echocardiography is less helpful in defining the presence of other left-sided cardiac valve disease. Dense additional echoes within the aortic root in the area of the aortic leaflets favor the presence of aortic stenosis but the severity of the stenosis cannot be determined from this finding alone.[64,65] The additional presence of concentric left ventricular hypertrophy strongly favors a severe degree of obstruction at the aortic valve.

Simultaneous pulse tracings and phonocardiography can provide objective confirmation of severe aortic stenosis. In the absence of heart failure, the left ventricular ejection time is usually prolonged, the carotid upstroke slowed and the peak of the basal ejection murmur delayed.[66–68] When these three findings were combined, Bonner et al.[67] reported a 96 percent specificity for the presence of severe aortic stenosis. The presence of only one of these findings usually indicates severe stenosis but by itself is usually not sensitive enough to identify all patients with severe aortic obstruction.

Aortic regurgitation: Mitral and aortic regurgitation can also be recognized with echocardiography but severity must once again be inferred from associated findings. High frequency diastolic vibration of the anterior mitral leaflet is commonly present in all degrees of aortic regurgitation.[69] In acute severe aortic regurgitation, early coaptation of the anterior and posterior mitral leaflets indicating premature mitral closure is a highly reliable sign of wide open regurgitation.[70,71] However, because this is not the most common form of aortic insufficiency encountered clinically, the sign is of limited value. In chronic aortic regurgitation, the amount of left ventricular dilatation determined from the left ventricular internal diastolic dimension provides an index to the severity of the regurgitant lesion.[72]

Mitral regurgitation: Mitral incompetence may or may not be directly recognized from the echocardiographic pattern of mitral leaflet motion, depending on the specific form of regurgitation present. Echocardiography has provided anatomic confirmation of late systolic prolapse of either or both mitral leaflets in the systolic click-murmur syndrome and has demonstrated flail leaflets in cases of ruptured chordae tendineae.[73–78] Although echocardiography has shown that mitral valve prolapse is more prevalent than previously appreciated, such prolapse is not found in the majority of patients with mitral regurgitation; moreover, the severity of regurgitation can only be inferred from the presence of combined left atrial and left ventricular dilatation.[78]

In summary, echocardiography is extremely helpful in placing our assessment of cardiac valve disease on a more objective basis without the need for invasive studies. It would appear possible to avoid cardiac

catheterization in patients with evidence of idiopathic hypertrophic subaortic stenosis unless they are clearly unresponsive to medical management. Similarly, there is hope that with more prospective studies and refinement of planar imaging techniques the severity of mitral stenosis will be accurately predicted, thus avoiding the need for cardiac catheterization completely or at least until the presence of moderately severe stenosis is confirmed. Further refinements in echocardiographic resolution and its systematic application in controlled prospective studies will be needed before the severity of aortic stenosis can be assessed accurately in large patient populations. Similarly, more specific criteria must be established for the assessment of regurgitant and combined valve lesions.

Pulmonary Embolic Disease (Lung Scanning)

The lungs lend themselves well to study of regional function with radioactive tracer techniques. Indeed, the practice of pulmonary scanning is one of the well established areas where definitive action is often taken on the basis of the results of radionuclide imaging.[79–81]

False negative lung scan: Several studies, including the Urokinase Pulmonary Embolism Trial, have shown that a normal lung scan makes it very likely (probability close to 100 percent) that *no* pulmonary embolism is present.[81–83] Theoretically, a large proximal embolus in the main pulmonary artery may affect equally the regional pulmonary circulation and hence yield a false negative scan. In practice, this has not been observed. In the Urokinase Pulmonary Embolism Trial, there were 10 patients with a large proximal embolus in the main pulmonary artery; no lung scan was falsely negative.[83] In this setting the estimation of perfusion deficit by scanning was usually less than expected on the basis of the angiographic finding.

Specificity of positive lung scan: Abnormal lung scans are more problematical since all pulmonary diseases can lead to abnormal scans. How specific is lung scanning in diagnosing pulmonary embolism? This question can be examined in the following manner: First, patterns of perfusion as shown in lung scans in the various pulmonary diseases have certain characteristics,[84–89] such as peripheral concave defects in pulmonary embolism, redistribution of blood flow in pulmonary venous hypertension and the fissure sign in congestive failure. Second, the diagnostic specificity of lung scanning is enhanced by a chest roentgenogram performed in conjunction with the scan. A concave peripheral perfusion defect in the presence of a normal chest roentgenogram is most likely due to pulmonary embolism. In a recent study[79] in which the scan perfusion defects were classified according to high or low probability of having been caused by pulmonary embolism, interpretations indicating embolism were confirmed by angiogram in 75 percent of cases. When the scan interpretation was normal, the angiogram was also normal. Third, in combination with the xenon-133 ventilation study, an abnormal lung scan in the presence of a normal ventilation study is virtually diagnostic of pulmonary embolism. On the other hand, in a patient with an abnormal perfusion lung scan and matchingly abnormal ventilation study, pulmonary embolism is less likely but cannot be absolutely excluded.[90–92] There may be underlying disease such as chronic obstructive lung disease not apparent in the plain chest X-ray film.

More recent data also suggest that in patients with suspected pulmonary embolism who have an abnormal perfusion scan and evidence of deep leg vein thrombosis documented noninvasively with electrical impedance plethysmography, there is a 90 percent probability that they have acute pulmonary embolism.[93]

Diagnostic specificity: In virtually all patients, normal perfusion lung scan excludes pulmonary embolism, and no further pursuit of the diagnosis is required. Similarly, in patients who have an abnormal scan and objective confirmation of phlebitis, particularly in the absence of roentgenographic findings of chronic lung disease, the probability is greater than 90 percent that they have acute pulmonary embolism. When a xenon-133 ventilation study is available, diagnostic specificity may increase. With these factors in mind, it is possible now to limit the application of pulmonary angiography to patients who do not meet these criteria or who have coexisting pulmonary embolism and chronic obstructive lung disease.

Congenital Heart Disease

Both nuclear techniques and echocardiography can be used to detect many congenital heart lesions. A detailed description of these applications is given in another article in this series[94]; some general principles will be outlined here.

Nuclear techniques: These have been used successfully to detect intracardiac shunts. After intravenous injection of a radionuclide the early appearance of radioactivity in a detector located over the systemic circulation indicates the presence of a right to left shunt. For this purpose, many prefer to use substances completely excreted or trapped by the lung, such as radioactive xenon or microspheres. The appearance of radioactivity in the systemic circulation shortly after intravenous injection indicates a significant right to left intracardiac shunt.[95,96] Similarly, early reappearance of radioactivity in the selectively monitored lung suggests left to right shunting.[97,98]

Nuclear angiocardiograms can aid considerably in the definition of selective cardiac chamber enlargement as well as the recognition of complex interrelations of the great vessels and of intracardiac shunts.[99,100] This technique is particularly useful in evaluating cyanotic neonates, in whom the risk of cardiac catheterization is considerable.

Echocardiography: This method plays an increasingly important role in the diagnosis of congenital heart lesions. Since the technique allows recognition of anatomic continuity of intracardiac structures, the relation of the great vessels with the ventricular chambers, valve

abnormalities and structural defects within the interventricular septum can be recognized by this means. To date, more than 30 distinct congenital abnormalities have been identified with echocardiography.[101]

In an adult population the congenital lesion that most often passes unnoticed is the atrial septal defect. Although such a lesion still requires right heart catheterization to confirm its presence, echocardiography appears to be extremely sensitive in detecting evidence of significant left to right shunting with this defect.[102–104] Thus, the presence of an enlarged right ventricular internal dimension with or without septal paradoxical motion should raise the question of right ventricular volume overload. This finding is not specific for an atrial septal defect because it may occur with other conditions such as tricuspid regurgitation, anomalous pulmonary venous connection and, occasionally, pulmonary hypertension. However, the absence of a significantly increased right ventricular internal dimension would appear to exclude a clinically significant left to right shunt on the basis of an uncomplicated interatrial septal defect.

Miscellaneous Problems

Pericardial effusion: Both echocardiography and nuclear techniques lend themselves to the evaluation of an enlarged cardiac silhouette. Whereas the majority of patients with this roentgenographic finding have cardiomegaly, the presence of a pericardial effusion is a not uncommon differential diagnostic problem. Echocardiography appears particularly sensitive to this condition since the separation of a nonmoving posterior pericardium from a moving adjacent epicardium can be detected even with very small effusions if care is taken with proper instrumental settings and technique to discern the posterior pericardium at the appropriate anatomic level.[105,106] By routinely performing echocardiography 24 hours before cardiac surgery, Horowitz et al.[107] recently showed that effusions as small as 15 ml could be detected The overlap of negative and positive patterns in their group of 41 patients was small, thus attesting to the specificity of the method as well.

Recently, features of cardiac tamponade have been demonstrated with echocardiography.[108] With inspiration there is an increased right ventricular dimension consistent with filling of this chamber. Concomitantly there is decreased excursion of the anterior mitral leaflet and diminished left ventricular dimension, indicating poor transmitral flow. These findings are in accord with the physical finding of a paradoxic pulse.

By radiolabeling the intracardiac blood pool large effusions can also be inferred from the discrepancy of this blood mass with the apparent size of the cardiac silhouette as well as its separation from the liver.[109] Effusions have also been demonstrated by ^{99m}Tc pertechnetate flow studies in which the cardiac blood pool is separated from the lungs by the fluid-filled pericardium to an abnormal degree.[110] Nuclear techniques are less sensitive[111] and less versatile than echocardiographic techniques which can be performed at the patient's bedside, but pericardial effusions may be observed during nuclear angiography or ventricular function studies with ^{99m}Tc albumin.

Dissecting aneurysm of the ascending aorta: This is an acute medical emergency. Recent reports[112–114] have shown that echocardiography can distinguish the cavity of the dissecting hematoma from the true aortic lumen. However, in none of these studies has the patient series from a single institution been large enough to establish definitely the diagnostic accuracy of the method. Moreover, false positive results have been reported.[115] Further evaluation is necessary before we can be certain of the reliability of ultrasound as a screening technique for the presence of this lesion.

Left atrial myxoma: The diagnosis of this tumor was virtually impossible to establish noninvasively before the advent of echocardiography. Such tumors, while rare in occurrence, have been repeatedly detected with this method by independent observers.[116–119] The presence of a radiodense area within the left atrium particularly prolapsing into the mitral funnel during diastole, appears to be pathognomonic for the presence of the tumor. With appropriate attention to proper instrumental settings, the false positive detection of this lesion by an experienced echocardiographer should be quite rare. False negative results can occur, but their true incidence may never be known in view of the relative infrequency with which this lesion is encountered Right atrial myxomas have also been recognized, particularly when prolapsing into the right ventricle.[11] Atrial myxoma has also been detected with scintiphotographic imaging.[120,121]

Intracardiac thrombosis: Left atrial clots in mitral stenosis and left ventricular thrombi in ventricular aneurysm and cardiomyopathy have been detected by the use of iodine-131 fibrinogen as well as radiolabeled fibrinolytic agents.[122] Here, too, the reported series are too small to make definitive statements at this time as to the clinical usefulness of such radionuclide screening techniques.

Conclusions

The past decade has seen considerable progress in the development of diagnostically accurate noninvasive cardiovascular procedures for recognition of major problems in adult medicine. Particularly notable is our ability to deal with pulmonary embolism in the majority of cases without resorting to pulmonary angiography On the opposite end of the spectrum, we are just beginning to define methods that show significant impairment of myocardial perfusion or myocardial damage, or both, as a result of coronary artery disease. Between these two extremes, we are able to identify qualitatively, and in some cases semiquantitatively, the presence and severity of specific forms of cardiac valve disease. In light of this progress it is hoped that in the future our reliance on invasive means of cardiovascular diagnosis can be limited almost exclusively to patients who are most likely to benefit from cardiac surgery toward which cardiac catheterization and angiography are integral steps.

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Common Procedures for the Noninvasive Determination of Regional Myocardial Perfusion, Evaluation of Regional Wall Motion and Detection of Acute Infarction

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A brief description is given of imaging techniques to record and analyze the myocardial perfusion scan, study changes in segmental wall motion, measure ejection fraction and ventricular volumes and detect acute myocardial infarction. Attention to the details of collimation, pulse height analyzer settings, intrinsic resolution of the imaging device and quality of the tracers utilized for these studies will permit information of high quality to be obtained from subjects with use of these noninvasive techniques.

Radioactive tracers can be used noninvasively to measure three important indicators of cardiac function: (1) regional distribution of myocardial perfusion, (2) total and regional ventricular contractility, and (3) presence or absence of acute myocardial infarction. To optimize the data that can be obtained from these measurements, one must be aware of both the physiologic factors controlling the distribution of tracer and the technical factors involved in recording the data and displaying them for interpretation by the clinician.

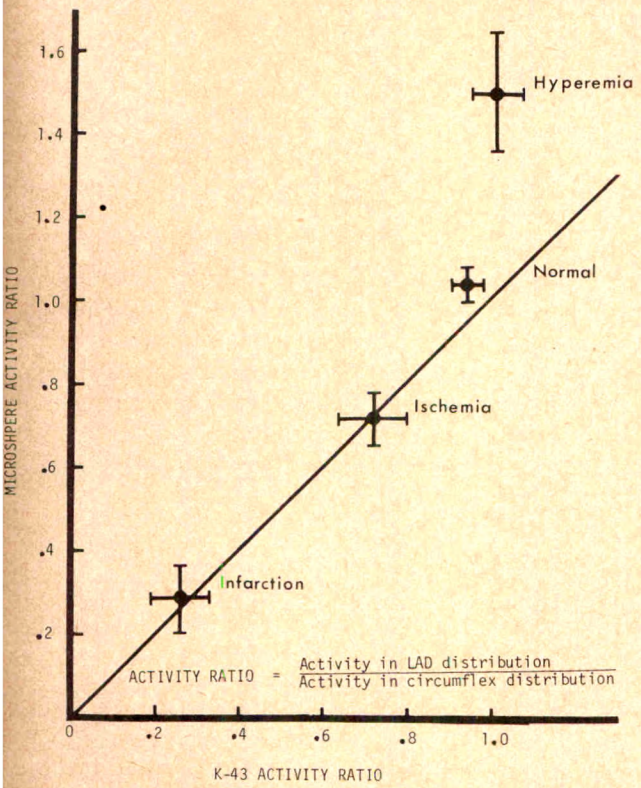
Myocardial Perfusion

The tracer: Ideally, myocardial perfusion should be assessed with a tracer that has the following properties: (1) no pharmacologic effects, so that physiologic conditions will not be distributed; (2) an extraction efficiency in the myocardium approaching 100 percent so that perfusion will be the major determinant of regional distribution; (3) rapid blood clearance, to reduce recirculation problems; (4) a gamma photon energy of 100 to 200 kev with no beta or beta-like radiation, to permit a high photon yield that is easily collimated, detectable with high efficiency and with a small radiation dose to the patient; (5) a physical half-life of 30 to 60 minutes, to permit multiple measurements over a short time span and to keep the radiation dose small; and (6) wide availability and low cost. No tracer now used for the noninvasive determination of regional myocardial perfusion meets all of these requirements. The monovalent cations, potassium, rubidium and thallium, which have been most widely used for the noninvasive determination of myocardial perfusion, have extraction efficiencies of 70 to 90 percent.[1,2] The blood concentration of these tracers 60 to 90 seconds after intravenous injection corresponds to less than 10 percent of the administered dose when the patient is given the injection under basal conditions.[2] As suggested by Sapirstein,[3] tracers that are extracted efficiently by an organ and have a relatively rapid blood clearance can be used for determining regional perfusion. Prokop et al.[4] compared the regional myocardial distribution of potassium administered intravenously with that of microspheres injected into the left atrium of dogs during normal coronary blood flow,

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ischemia caused by partial occlusion of a vessel and cardiac pacing, and total occlusion of a vessel. A linear relation was found between the myocardial distribution of perfusion as indicated by the microsphere injections and that indicated by the intravenous administration of potassium (Fig. 1). However, when flow was increased by reactive hyperemia, the increase in potassium concentration did not parallel that of microspheres. Under these conditions of high flow, the extraction efficiency of potassium appears to be reduced. Similar relations have been found with thallium-201[5] (Fig. 2).



IGURE 1. Ratio of activity in the experimental area compared with that ı the control zone of the myocardium as determined with microspheres ɔrdinate) and potassium-43 (abscissa). The **dots** represent the mean, nd the **bars** 2 standard deviations of the mean for these determinations. Reprinted from Prokop et al.[4] by permission of the American Heart ssociation, Inc.)

The concentration of tracer in the myocardium at a particular time after injection is influenced by the rate of turnover of the intracellular pool that these tracers enter in the myocardium. Potassium, for example, has a half-life in the myocardium of about 90 minutes,[6] whereas the half-life of thallium is considerably longer, probably about 7 hours (Weich H, et al: unpublished observations). As the interval between injection and the time of imaging increases, the regional distribution of tracer within the myocardium is increasingly influenced by the rate of intracellular turnover of the tracer. Therefore, whenever possible, the determination of regional myocardial perfusion should be made immediately after administration of the tracer.

The imaging device: The physical characteristics of the tracer and the resolution of the imaging device are also important in determining the quality of the images. Myocardial perfusion images can be recorded with either a rectilinear scanner or a scintillation camera[7] (Fig. 3). The rectilinear scanner has no field uniformity problems, and its resolution is limited primarily by the design of the collimator. High resolution collimators usually have less sensitivity than those with lower resolution. Therefore, to record an image with a preset count density, a longer time is required with a high resolution collimator than with one of low resolution. Because it is desirable to detect small lesions, a high resolution collimator should be used.

With the rectilinear scanner, spatial localization of the distribution of activity is achieved mechanically as the detector moves back and forth across the patient's body. The scintillation camera, on the other hand, views an entire field of activity simultaneously and determines the location of photons resulting from their interaction

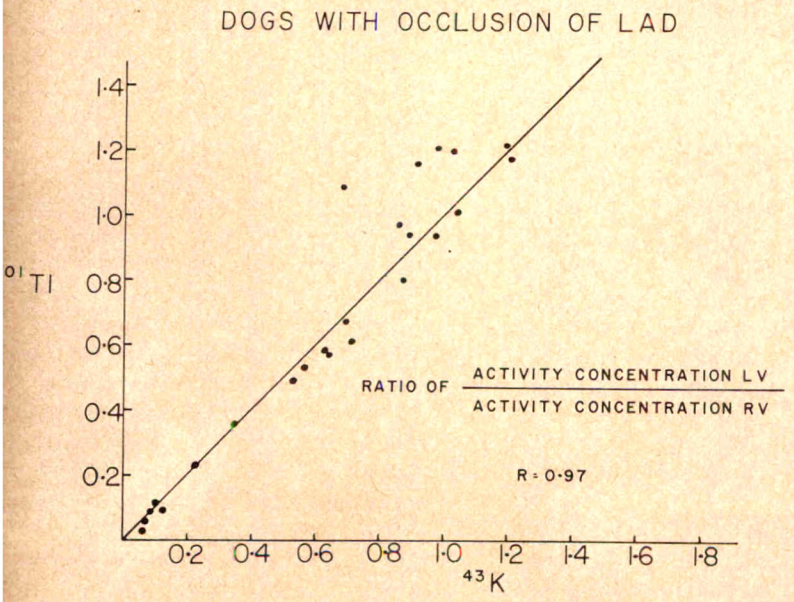


FIGURE 2. Activity ratio in a portion of the left ventricle (LV) compared with that in the right ventricle (RV) in dogs with occlusion of the left anterior descending coronary artery (LAD). Multiple samples were taken from tissues supplied by the left anterior descending coronary artery and those supplied by the left circumflex coronary artery and compared with tissue from the right ventricle after intravenous administration of thallium-201 and potassium-43. The ratio value for thallium is listed on the ordinate; that for potassium-43 on the abscissa. A correlation coefficient of 0.97 was found. (Reprinted from Strauss et al.[5] by permission of the American Heart Association Inc.)

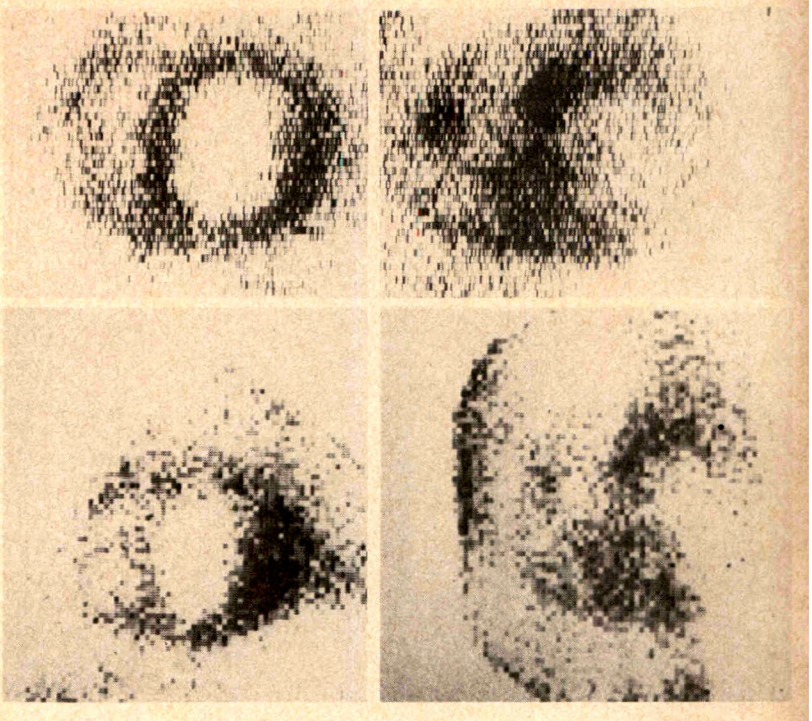


FIGURE 3. Myocardial perfusion images obtained with a rectilinear scanner **(top panels)** and scintillation camera **(bottom panels)** after the administration of thallium-201 in the left anterior oblique **(left panels)** and anterior position **(right panels).** Although there are minor differences in the appearance of the left anterior oblique views, the images obtained with the two instruments are quite similar. (Reproduced from Cook et al.,[7] with permission of the Society of Nuclear Medicine.)

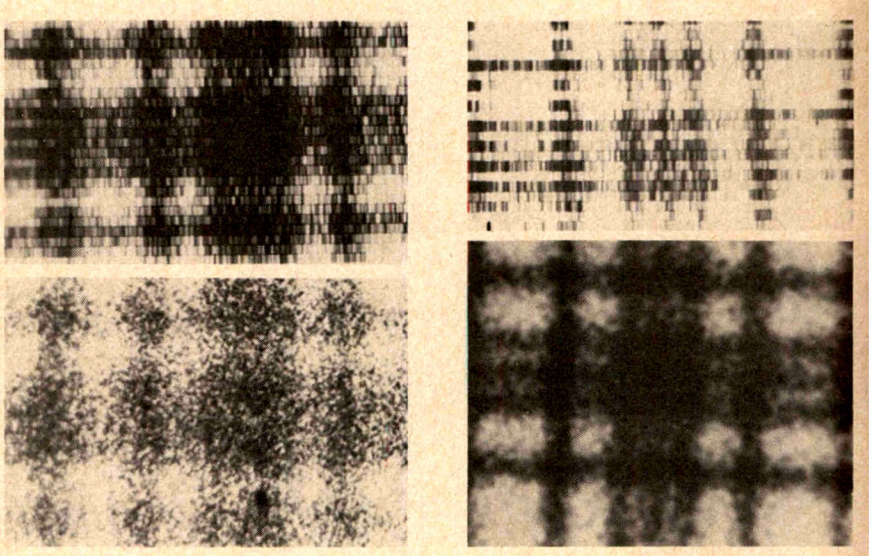


FIGURE 4. Phantom scans with rectilinear scanner **(top panels)** and scintillation cameras **(bottom panels)** imaging a grid source of activity with the central squares of 1 cm. **Left upper panel,** results with a medium resolution collimator and a rectilinear scanner; **lower left panel,** results with a 19 photomultiplier tube scintillation camera; **upper right panel,** results with a high resolution collimator on the rectilinear scanner; **lower right panel,** results with a high resolution scintillation camera with parallel hole collimator. (Reprinted from Cook et al.[7] with permission of the Society of Nuclear Medicine.)

in the sodium iodide crystal by generation of an electronic pulse. Localization of such signals becomes less certain as the photon energy decreases. At energy levels of less than 60 kev, commercially available scintillation cameras have too poor spatial resolution to be usable. As the photon energy increases (up to about 300 kev), the certainty of the positioning signals generated by the camera increases. Thus, for the scintillation camera, spatial resolution is primarily the result of two variables: (1) photon energy, and (2) collimator. In addition, the scintillation camera is subject to problems of field uniformity, that is, the sensitivity for detecting and positioning photons may not be uniform across the entire surface of the detector. This can cause artifacts and make images difficult to interpret. The nonuniformity should be minimized by proper maintenance of the camera and corrected whenever possible with a computer. Most collimators for the scintillation camera are designed to provide the best combination of sensitivity and resolution with lower energy tracers. These factors combine so that a nuclide that has an energy level of 100 to 200 kev, a rapid rate of blood clearance, high myocardial extraction efficiency and low concentration in the lung should be optimal for myocardial imaging. Thallium-201 meets most of these criteria, even though its 80 kev mercury X-ray is near the low end of the energy scale for resolution with the scintillation camera.

The importance of these factors to myocardial images can be demonstrated in the phantom study shown in Figure 4. The images were obtained with a rectilinear

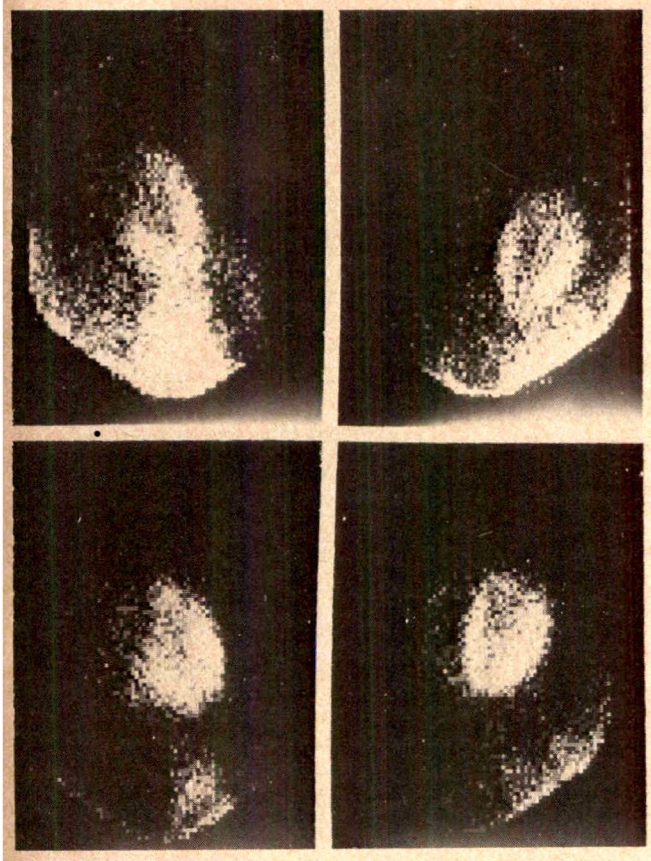


FIGURE 5. Thallium scan in a subject without coronary artery disease obtained in the anterior position **(left panels)** and left anterior oblique **(right panels)** with injection at rest **(upper panels)** and during stress **(lower panels).** The zone visualized is the left ventricular myocardium with associated left ventricular cavity. There is a hint of right ventricular myocardial activity seen on the stress scan in the left anterior oblique view. A zone of decreased tracer concentration at the apex is a normal variant. The tracer concentration of splanchnic activity is greatly decreased, in the stress study compared with that at rest.

scanner, using a medium resolution and high resolution collimator (upper panels) and images with a 19 photomultiplier tube scintillation camera (left lower panel) and high resolution (37 tube) scintillation camera (right lower panel). A marked difference in structural detail can be perceived in these images. The two images on the right side provide sufficient detail to define most myocardial lesions (the central squares are 1 cm apart), whereas the two on the left side, are inadequate for most clinical purposes. Thus, when recording the images, a high resolution collimator on a rectilinear scanner or a high resolution scintillation camera with high resolution collimator must be employed.

Since the left ventricular myocardium has an ovoid shape with a hollow center, it is necessary to record multiple views to increase the probability of detecting a perfusion defect. Phantom studies in our laboratory[7] have indicated that lesions were best defined when seen en face or in tangent. As the lesions were rotated to other positions, they were difficult or impossible to see. Since we do not know in advance where lesions will be located, these data suggest that images must be recorded in at least three positions and preferably four.

Imaging at rest and during stress: When thallium is administered to a patient at rest, zones of decreased perfusion or extraction efficiency can be detected. However, coronary lesions of 70 percent or less luminal narrowing will usually not be detected with tracer administered at rest because flow distal to the fixed obstruction may be normal and equal to that found distal to nonobstructed vessels. If a patient exercises or undergoes cardiac pacing so that myocardial perfusion is increased, the increase in flow to a region beyond a stenotic artery is less than the increase that occurs to normal zones. If tracer is administered during stress, its distribution in the myocardium will be determined by the distribution of perfusion during the time the tracer is cleared from the blood. Because activity differences in the myocardium will be seen only if sufficient flow differences are produced, it is important not to terminate the test if only S-T segment changes occur in the electrocardiogram. On the other hand, if the patient becomes symptomatic with severe anginal pain, the tracer should be administered immediately and the test terminated as soon as possible. If at all possible, it is desirable to continue exercise for at least 30 seconds after the administration of tracer so that normal myocardial perfusion will remain elevated during the period of tracer clearance from the blood. The type of stress appears to be less important than the severity of the stress. Many types of stress can cause changes in perfusion when a subcritical stenosis is present, as judged from both patient and animal studies including exercise,[8] pacing[4] and drug-induced stress.

There are striking changes in the myocardial perfusion image obtained at rest compared with that obtained during stress even in normal persons[7] (Fig. 5). With injection at rest, the left ventricular myocardium is well seen, whereas the right ventricular myocardium is barely seen or not seen at all. This is probably related to the differences in mass between the right and left ventricles in normal subjects: The right ventricular myocardium is 1/3 the thickness of the left and blood flow is about 10 percent per gram less than that of the left. Since the activity in the lung and chest wall is about 1/2 to 1/3 that of the left ventricle, it is not surprising that the right ventricle is invisible in most normal persons. Tracer distribution in the left ventricular myocardium is often somewhat nonuniform at rest, probably as a result of the heterogeneity of coronary blood flow. The variation in activity due to statistical fluctuation at the count rates usually recorded for myocardial imaging should only be a maximum of 6 percent in adjacent 1 cm segments, whereas the observed variation in activity in adjacent segments approaches 15 percent in normal subjects. No clear-cut zones of decreased tracer concentration greater than 1 cm in size were found in a group of 13 normal subjects studied at rest and during stress. There was a small zone of decreased tracer concentration in the region of the apex of the left ventricular myocardium in 11 of 13 normal subjects. Symmetrical regions of increased tracer concentration were seen in the areas of insertion of the papillary muscles, best seen in the left anterior oblique views.

There is a zone of decreased concentration in the center of the left ventricular myocardial image that corresponds to the left ventricular cavity.

Although tracer concentration in the lungs decreased 25 to 50 percent during exercise compared with rest, activity in the myocardium increased only 5 to 10 percent over that found at rest.[7] However, the heart was more clearly defined in the scan obtained during exercise because of the improved contrast between the myocardium and the surrounding lung. The distribution of tracer within the myocardium became more uniform and the right ventricular myocardium was visualized in 13 of 13 normal subjects. Blood flow to the splanchnic bed decreased with exercise, and the concentration of thallium seen in the liver and spleen was greatly reduced. In general, the images recorded with the tracer administered during stress are easier to interpret than those recorded with the tracer administered at rest.

Recording and processing the myocardial image: The myocardial scan is usually recorded on film, in a computer core or on magnetic tape or disk. When the data are recorded on film, it is not possible to vary contrast or carry out other useful data processing techniques after recording the image. Since the heart to background ratio is only 2 to 3:1, contrast enhancement of the images makes regions of decreased tracer concentration more obvious. High contrast film should be employed to magnify these small changes in activity into larger changes in film density. When a data processing system is used to record the images, contrast can be increased by the observer so that multiple contrast levels can be examined to optimize interpretation of the study without loss of the original data. A data processing system is the preferred means of data recording since observers can view the data under different conditions before giving a final interpretation.

Analysis of the myocardial perfusion scan: Once the images are recorded, the observer should examine them to determine the distribution of tracer throughout the left ventricular myocardium. Focal zones of decreased tracer concentration indicate focal areas of decreased perfusion or extraction efficiency. At this time, we are not aware of diseases that change only extraction efficiency, but it is possible that some cardiomyopathies such as those associated with muscular dystrophies are associated with normal flow and reduced extraction efficiency. To date, sarcoidosis has been shown to cause in some patients focal zones of decreased tracer concentration in the left ventricular myocardium.[9]

The thickness of the myocardium in the thallium-201 images should be measured. The normal left ventricular myocardial thickness is approximately 2 cm when these images are projected life-size. Conditions such as concentric hypertrophy cause an increase in the thickness of the left ventricular myocardium. Asymmetric thickening can occur in conditions such as idiopathic hypertrophic subaortic stenosis. In this condition, the septum has a triangular shape (with the apex pointing toward the aortic valve) and is considerably thicker than the posterior wall. Recent work done by Bulkley et al.[10] indicates that the scan can help make a specific diagnosis of idiopathic hypertrophic subaortic stenosis. The relative sensitivity of the scan compared with echocardiography has not been defined.

The size of the left ventricular cavity should also be estimated from the myocardial perfusion scan even though details of the endocardial surface are not well defined. Small changes in left ventricular size cannot be readily appreciated from these images, in part because the images are recorded throughout the entire cardiac cycle. In patients with marked dilatation of the ventricle, the cavity appears greatly enlarged. Therefore, the relative size of the left ventricular cavity can help to make the diagnosis of left ventricular dilatation.

The right ventricular myocardium is not usually defined in the scan obtained at rest unless there is marked right ventricular hypertrophy. Recent studies in our laboratory by Cohen et al.[11] suggest that the right ventricular myocardium can be seen when there is persistent right ventricular hypertension.

The relative tracer concentration in the liver should be compared with that in the left ventricular myocardium to determine the status of splanchnic blood flow at the time of tracer administration. If there is marked tracer concentration in the liver, it is probable that the tracer was injected during the basal or resting state. During exercise stress, splanchnic blood flow is greatly diminished and the liver is not visualized.

Zones of decreased tracer concentration: It is most helpful to compare the scan obtained in the resting basal state with that obtained during maximal stress. In normal subjects, the tracer distribution in the myocardium is homogeneous and unchanged from rest to stress. Appearance of new or enlarged areas of decreased tracer concentration or areas with more severely decreased tracer concentration make it highly likely that myocardial ischemia has developed in regions not as apparent at rest. Regions of abnormal blood flow found in a rest scan that do not change when tracer is administered during stress are referred to as "fixed abnormalities" of perfusion. When the scan obtained at rest is the only examination performed, zones of decreased tracer concentration can be caused by either a "transient" or a "fixed" abnormality of perfusion.

Regional Wall Motion Measurements

The tracer: These procedures are used to evaluate the size, shape and position of the cardiac chambers. The test is performed utilizing a tracer that remains only in the blood pool and that does not visualize the myocardial muscle. Tracers such as technetium-labeled red cells or technetium-labeled albumin have both been used in this test.[12,13] Technetium-labeled albumin has the advantage of requiring preparation only once a day and is suitable for use in any patient, whereas technetium-labeled red blood cells require the patient's own blood to be drawn, individually labeled and then readministered. Although labeling with this method is tedious and time consuming, the label remains on the cells and does not diffuse into the extravascular compart-

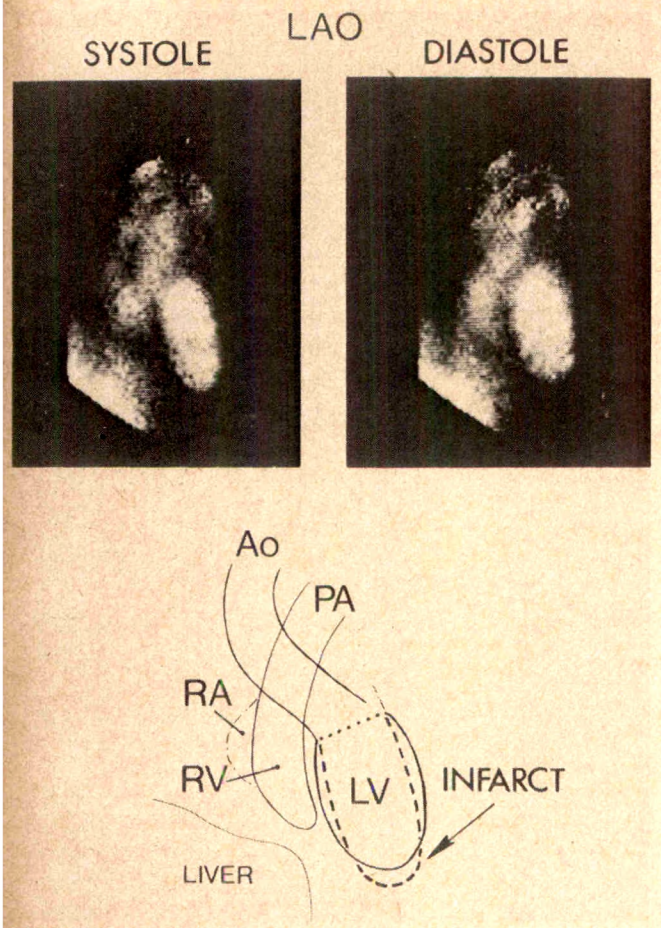


FIGURE 6. Gated blood pool scan in the left anterior oblique (LAO) position in a patient with an aneurysm of the left ventricle. End-systole at **left,** end-diastole at **right.** Diagram showing the left ventricular borders at end-systole indicated by the **dotted line** and end-diastole by the **solid line** is shown below. Ao = aorta; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle.

ment during the time of measurement. Technetium-labeled red blood cells are therefore a more suitable tracer for this study than technetium-labeled albumin although the latter can be used quite successfully for most clinical measurements.

Ejection fraction: first pass method: Ejection fraction can be calculated from information recorded either during the first passage of tracer through the heart[14] or after the tracer has equilibrated in the vasculature.[15] The first pass method provides a recording of the time-activity curve over the left ventricle that has peaks and valleys corresponding to the filling and emptying of the chamber. After a correction is made for background activity, the peaks of the curve correspond to the activity in the chamber at end-diastole, the valleys to that at end-systole. The ejection fraction can readily be calculated from the counts at these points. The difficulty with the method is that only a limited number of counts are recorded during these short portions of the cardiac cycle. To achieve a satisfactory level of precision, the data from three to five cardiac cycles are summed point by point, and the resultant higher count density curve is fitted with a smoothing function and the ejection fraction is calculated. Several investigators[16] have reported high correlations with ejection fraction calculated at angiography. Because the method requires only a very short measurement time, it can be applied to patients under very unstable conditions. The limitations of the method are that only one measurement can be made from a single injection of tracer, and it is difficult to obtain high resolution information about regional wall motion from these images.

Ejection fraction: gated technique: An alternate means of obtaining information about ejection fraction and regional wall motion utilizes a physiologic trigger and the scintillation camera so that images are recorded during specific portions of the cardiac cycle.[15] This system has several advantages: (1) Images can be recorded for high count density to permit detailed evaluation of regional wall motion; (2) multiple positions can be examined after a single injection of tracer; (3) ejection fraction can be calculated either digitally from changes in counts in the regions of the chamber or in analog fashion tracing the outlines of the left ventricular chamber at end-systole and end-diastole and utilizing the geometric assumptions of Sandler and Dodge to calculate left ventricular volumes and ejection fraction. Fletcher et al.[16] comparing the first pass technique with the gated technique utilizing the counts method found that the two methods provided similar data regarding ejection fraction (correlation coefficient greater than 0.9). It is important when performing these examinations to utilize a high contrast film or a mode of data display that permits adjustment of the contrast since the activity ratio between the left ventricle and background is usually less than 3:1. This means that it may be difficult at times to precisely identify the border of the chamber when a low contrast display or film is utilized. A high contrast film sharpens the apparent difference between the left ventricular chamber and background.

A high resolution collimator should be used to record these images since it is desirable to obtain precise measurements of small changes in regional wall motion. The number of events recorded in the image is an important factor in determining how well the borders of the ventricles can be defined. The best compromise between the time required to obtain the data and the optimal amount of data needed to define precisely the left ventricular borders seems to be that approximately 500,000 counts should be collected in the entire image.

Region wall motion changes: The borders of the cardiac chamber as seen in the end-systolic and end-diastolic images are traced and superimposed to define regional wall motion changes. Radii from the geometric center of the left ventricle to the borders, except those adjacent to the valve planes, usually contract approximately 20 percent of their length from end-diastole to end-systole. If this degree of shortening does not occur, hypokinesia is present. Correlations of the results of contrast ventriculography and tracer methods indicate that the latter can adequately define regional wall mo-

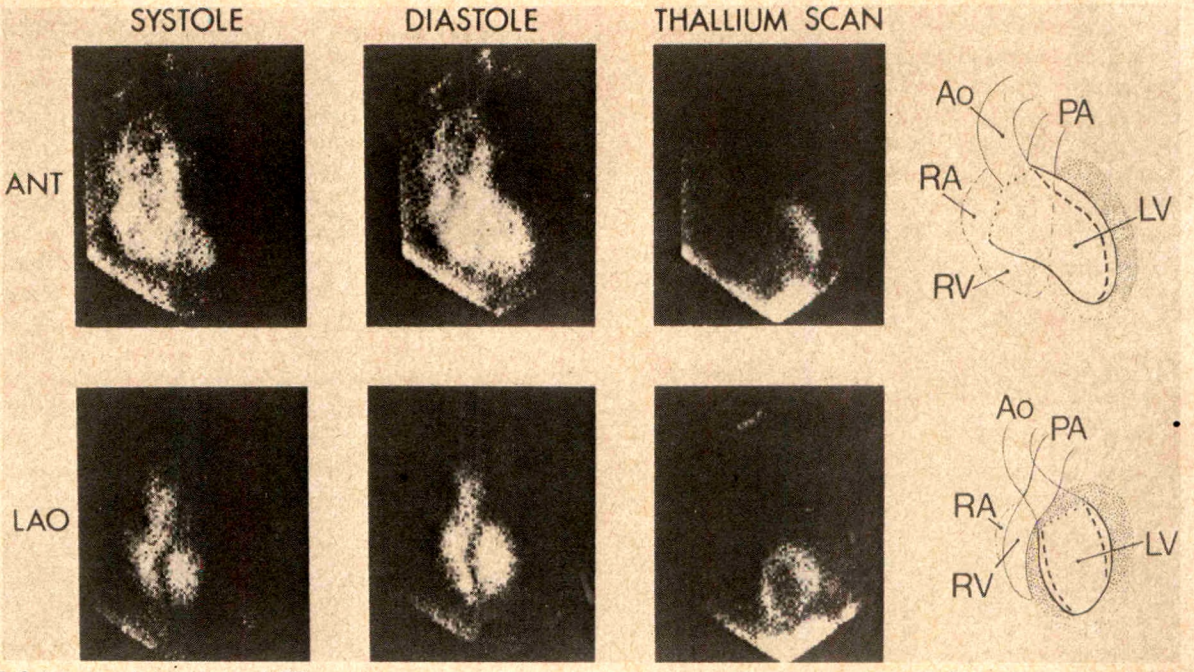


FIGURE 7. Gated scans in the anterior (ANT) position at end-systole and end-diastole **(top left and top middle panels),** and thallium scan in this position **(top right panel).** Gated scans in the left anterior oblique (LAO) position at end-systole **(bottom left),** end-diastole **(bottom center)** and thallium scan in this position **(bottom right).** Traced outlines of the left ventricular chamber at end of diastole are shown by the **solid line** while those at end-systole are shown by the **dotted line** in the diagrams at right. The thallium scan is indicated by the **shading** outlining the end-diastolic volume. There is no wall motion in the area where there is decreased thallium concentration involving the inferior wall in the anterior view and the posterolateral surface in the left anterior oblique view. Abbreviations as in Figure 6.

tion abnormalities. For example, Rigo et al.[17] and Zaret et al.[8] observed high correlations between abnormalities in regional wall motion and tracer examinations (Fig. 6). An effective means of perceiving changes in regional wall motion is to display an end-systolic image alternately with the end-diastolic image on one screen. When the data are displayed in this manner, one can readily perceive changes in regional wall motion and the regions moving poorly or paradoxically are accentuated. This type of data display is better than simply tracing the borders of the ventricles and superimposing them.

Recording the data at only two points in the cardiac cycle does not take advantage of all the photons that emanate from the patients. If data are recorded continuously in list mode in synchrony with the electrocardiogram for 15 or 20 minutes, the data can be displayed in multiple frames, as suggested by Green et al.[18] When this is done, the first 20 msec after the R wave in each cardiac cycle are sought by the computer and entered into one frame. Thereafter, subsequent 20 msec frames following the R wave are framed into a series until the entire cardiac cycle has been examined. The procedure results in an average cardiac time-activity curve recorded over the 20 minutes of data acquisition. Each image in the average cardiac cycle is of high count density, and precise borders can be drawn around the left ventricle. With this approach, high resolution images of each point in the cardiac cycle can be obtained. If a region of interest is selected over the left ventricle using a computer system, a quantitative left ventricular time-activity curve can be generated from these data.

Ventricular volumes: The gated blood pool scans are also interpreted by tracing the outlines of both the left and right ventricles in the anterior and left anterior oblique positions and calculating the volumes of the chambers. Volumes can be calculated from the activity in the ventricle and a blood sample drawn and counted in a suitable phantom; activity in the chamber is determined after background correction; then, the left and right ventricular volumes can be calculated directly. An alternative approach that has proved satisfactory is to outline the left ventricular chamber and calculate volumes according to the formula of Sandler and Dodge. We estimate right ventricular volume by comparing the area of the right ventricular chamber in the left anterior oblique position with that of the left ventricular chamber. The projection of the right ventricular chamber is ordinarily about 10 percent larger than that of the left.[19] Although there is a slight error introduced into the volume calculation using the standard biplane formula of Sandler and Dodge when the two views are not 90° apart, this error does not appear to be too great for clinical examinations. In addition to volumes, the ejection fraction of the ventricle and the regional wall motion are quantified. Regional wall motion abnormalities are usually expressed as percentage of the total left ventricular free wall circumference.

It is particularly important in patients with diffuse hypokinesia to determine whether the gating was accomplished correctly. There are several ways to tell how effective the gating was. Changes in right ventricular volumes can be seen when the left ventricular chamber

barely moves; changes occur in the right or left atrium; and, finally, we can record the exact intervals after the R wave that gating occurred.

One major advantage of tracer techniques is the relative safety and ease of performing repetitive studies. The gated and myocardial perfusion scans can readily be performed together in the same patient and provide two pieces of information that reinforce each other: the state of myocardial perfusion and the function of the left and right ventricles. These data can be used effectively to help determine which patients may benefit from coronary bypass surgery (Fig. 7).

• Acute Myocardial Infarct Imaging

This technique is based on the principle that acutely damaged tissue is associated with abnormalities in the cell membrane that permit entry of tracers ordinarily excluded from the cells. Once in the cell, these substances bind to either damaged proteins or excessive quantities of calcium or, possibly, other substances not yet clearly defined. For the tracer to reach the damaged tissue, there must be some residual blood flow into the area.[20] The concentration of these tracers in the zone of damaged myocardium is quite low, so that blood must be totally cleared of this material before an adequate image can be obtained. This means that the patient must have a good renal function. A high resolution collimator should be employed and the images should record a minimum of 350,000 counts in the total field. It is important that multiple views be recorded for best localization of the lesion. Minor amounts of increased tracer concentration or vague areas of increased uptake are probably not significant. Areas of increased uptake should be well defined and have an activity equal to or greater than that of the ribs.

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Myocardial Perfusion Imaging and Gated Cardiac Blood Pool Scanning: Clinical Application

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Myocardial perfusion imaging with thallium-201 and gated cardiac blood pool scanning are finding increasing use in clinical cardiology. These noninvasive techniques have been found useful in detecting myocardial infarction independent of the electrocardiogram and determining the site and extent of the infarct as well as its effect on left ventricular function. These studies provide important prognostic data and are proving to be of value in evaluating patients with cardiogenic shock. Neither the thallium-201 myocardial perfusion image nor the gated cardiac blood pool scan can distinguish between acute and chronic myocardial damage. In clinical situations where this is important, infarct avid imaging with technetium-99m pyrophosphate allows determination of whether a given perfusion defect or wall motion abnormality is acute.

Myocardial perfusion imaging with thallium-201 at rest and after exercise is also proving to be of value in evaluating patients with suspected ischemic heart disease. Initial studies suggest that the technique may be more sensitive than exercise electrocardiography and is of special value in minimizing the occurrence of false positive exercise tests for the diagnosis of ischemic heart disease. The combined tracers technique is also of value in the evaluation of patients undergoing coronary bypass graft surgery and those with cardiomyopathy.

The techniques of myocardial perfusion imaging and gated cardiac blood pool scanning are finding increasing use in clinical cardiology. The technical details and limitations of these procedures are described elsewhere in this Symposium.[1] This report will review the clinical applications of these procedures.

Myocardial Infarction

Most patients admitted to the coronary care unit with a history suggestive of acute myocardial infarction have other laboratory evidence of infarction, such as an elevated serum creatine phosphokinase level or typical electrocardiographic changes, or both. In some, however, the history may be suggestive but not diagnostic. The electrocardiogram may show only ST-T wave changes or an interventricular conduction defect of the left bundle branch block type or, on occasion, may be entirely normal. Creatine phosphokinase levels, although usually elevated in acute myocardial infarction, may not be abnormal early in the course of infarction. In a patient with no previous myocardial infarction, the detection of a myocardial perfusion defect in the thallium-201 myocardial perfusion image[2–4] and a wall motion abnormality in the gated cardiac blood pool scan[5,6] (Fig. 1) is suggestive of acute myocardial infarction.

Transmural versus nontransmural infarction: Almost all episodes of transmural myocardial infarction can be identified immediately by the finding of a thallium-201 myocardial perfusion defect and evidence of abnormal regional myocardial wall motion in the gated cardiac blood

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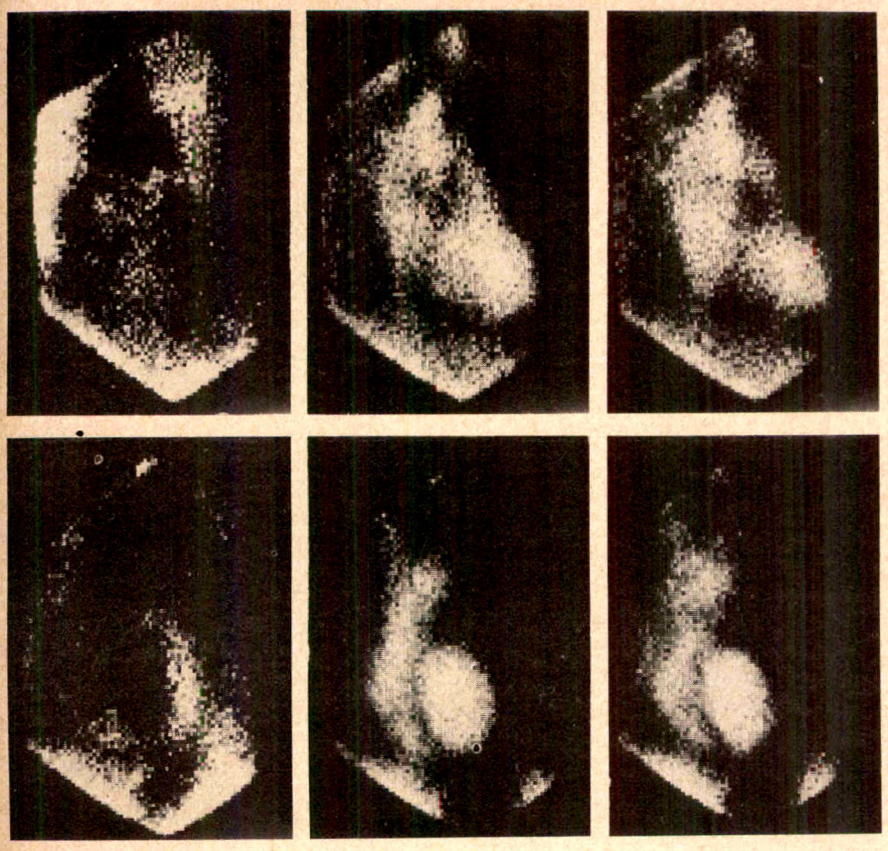


FIGURE 1. Previously asymptomatic patient with electrocardiographic evidence of an acute anteroseptal myocardial infarction. **Top row (from left to right):** anterior thallium-201 myocardial perfusion image; anterior end-diastolic gated cardiac blood pool image and anterior end-systolic gated cardiac blood pool image. **Bottom row:** left anterior oblique images in same sequence as on top. Note a perfusion defect in the anterior apical (anterior view) and apical septal (left anterior oblique) regions of the myocardium in the thallium-201 image. The gated cardiac blood pool image reveals decreased left ventricular function and akinesia of the anterior apical and septal areas of myocardium corresponding to the perfusion defect seen in the thallium-201 image.

pool scan. An acute nontransmural myocardial infarction may not be detected so readily. The perfusion defect in this condition may not be apparent after the first few hours[7] because scattered areas of viable myocardium may be interspersed with acutely ischemic areas, and there may not be a sufficient gradient between normal and ischemic or infarcted myocardium to appreciate a perfusion defect. The gated cardiac blood pool scan, on the other hand, may reveal an area of abnormal myocardial wall motion in patients with acute nontransmural infarction even after the first few hours when the thallium-201 myocardial perfusion image may be normal or equivocal (Fig. 2). In these patients, the mass of ischemic myocardial cells may not be sufficient to allow appreciation of a perfusion defect. A wall motion abnormality may, however, result from a disruption of the functional integrity of the myocardium, which is dependent upon the viability of all of the myocardial cells within a given perfusion area. Initial studies suggest that almost all patients with a nontransmural myocardial infarction have evidence of a wall motion abnormality in a gated cardiac blood pool scan.[6]

Acute versus old infarction: Neither the thallium-201 myocardial perfusion image nor the gated cardiac blood pool scan can distinguish between acute and chronic damage. In a patient with a previous myocardial infarction the finding of a perfusion defect or an abnormality of regional myocardial wall motion is therefore not diagnostic of acute damage. To determine whether a perfusion defect or wall motion abnormality is acute, other data such as serial electrocardiographic or enzyme studies or infarct avid scanning with technetium-99m pyrophosphate or glucoheptonate must be performed.[8,9]

Determination of infarct site: In patients with acute myocardial infarction confirmed by electrocardiographic or serum enzyme changes, or both, there may also be a role for myocardial imaging. Both the thallium-201 myocardial perfusion image and the gated cardiac blood pool scan allow an independent estimation of the localization and extent of the myocardial infarction.[2,3,6] The electrocardiographic correlations with the site of infarction are at best only fair.[10] Both the thallium-201 image and the gated scan show excellent correlation with the site of infarction as determined by the finding of an akinetic area in the left ventricular contrast angiogram.[11]

Determination of infarct size: Determination of infarct size on the basis of creatine phosphokinase (CPK) release has been shown to be clinically useful in predicting the extent of left ventricular dysfunction and survival after myocardial infarction.[12] Although experience is limited, such determination correlates well with postmortem estimates of infarct size[13] but requires serial study over 48 to 72 hours. To be of optimal value, estimation of infarct size should be available immediately. Although an abnormality in both the thallium-201 myocardial perfusion image and the gated cardiac blood

pool scan reflects both ischemia and infarction, the information is available immediately and may allow appropriate therapeutic decisions to be made early when they will have maximal benefit. In a study by Rigo et al.,[6] there were significant differences between survivors and those dying from acute myocardial infarction in left ventricular ejection fraction and percent of left ventricular myocardium that was infarcted, as estimated from the percent of akinesia and left ventricular ejection fraction indicated by the gated cardiac blood pool scan. In their study as in others there was also a significant difference in serum CPK release between those surviving and dying. CPK release, however, reflects only acute damage. In a patient with a previous myocardial infarction even a relatively small acute infarct may cause sufficient damage to result in myocardial failure or death. To determine prognosis in acute myocardial infarction, a measure of the perfusion and function of the remaining viable myocardium would be most appropriate. Both the thallium-201 myocardial perfusion image and the gated cardiac blood pool scan allow such measurement and therefore should play an increasingly significant role in early evaluation of prognosis as well as diagnosis of acute myocardial infarction.

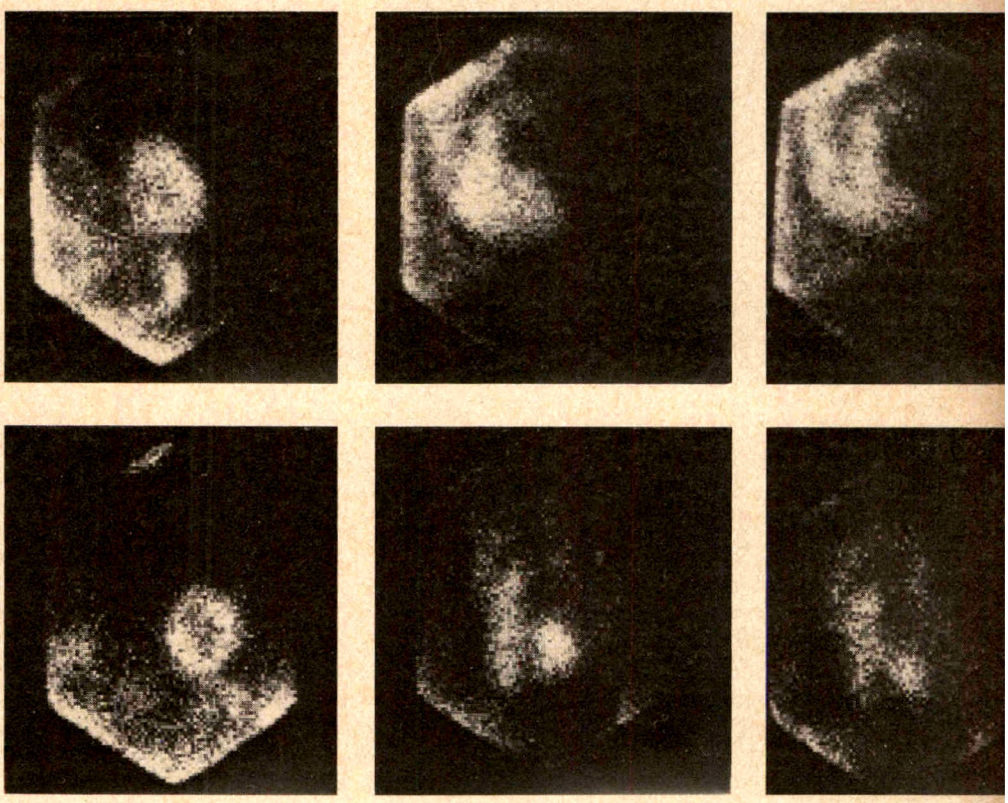


FIGURE 2. Patient with electrocardiographic evidence of an old anterolateral nontransmural infarction. **Top row (from left to right):** anterior thallium-201 myocardial perfusion images, anterior end-diastolic gated cardiac blood pool image and end-systolic gated cardiac blood pool image. **Bottom row:** left anterior oblique images in the same sequence as on top. Note the normal thallium-201 images. Analysis of the gated cardiac blood pool images reveals good septal motion (left anterior oblique view) but an area of apical (anterior view) and lateral akinesia (left anterior oblique view) suggesting myocardial damage.

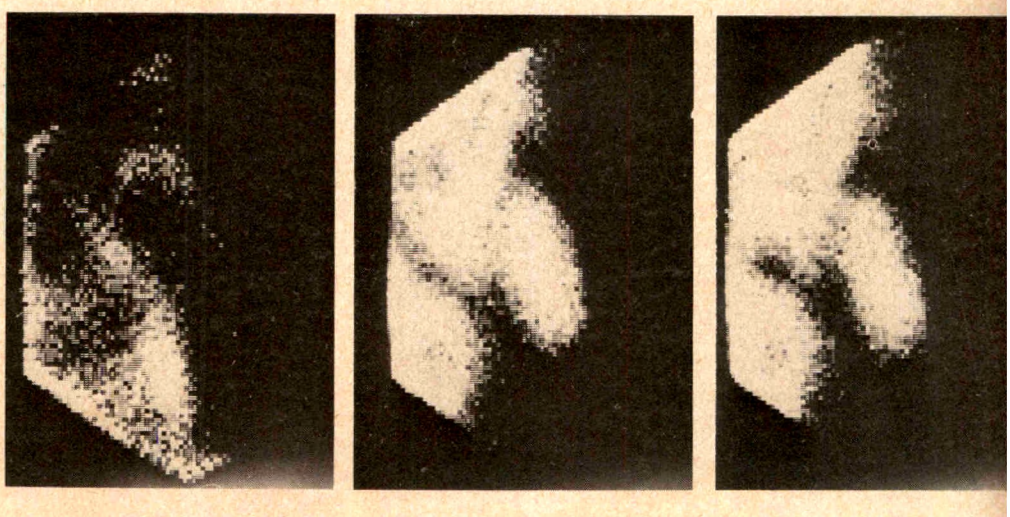


FIGURE 3. Patient with electrocardiographic evidence of an acute anterior myocardial infarction and cardiogenic shock. **From left to right:** anterior thallium-201 myocardial perfusion image, anterior end-diastolic gated cardiac blood pool image and anterior end-systolic gated cardiac blood pool image. Note the large anterior apical defect in the thallium-201 image and an enlarged poorly contracting left ventricle with anterior apical akinesia in the gated cardiac blood pool image. The right ventricle (seen best in the left anterior oblique view, which is not shown) was not enlarged.

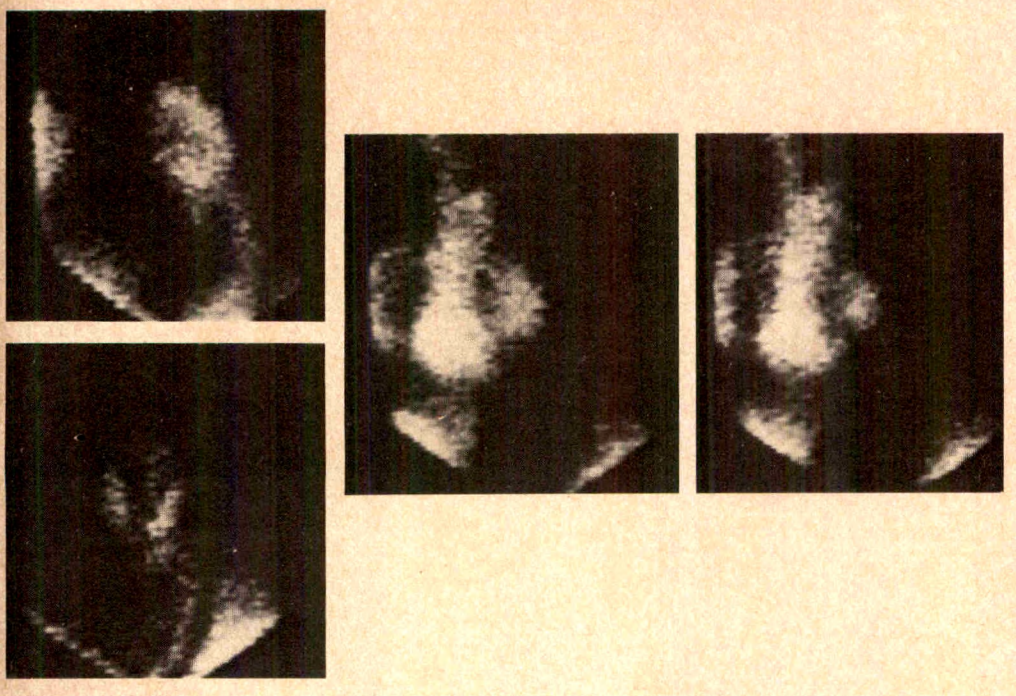


FIGURE 4. Patient with electrocardiographic evidence of an acute inferior myocardial infarction and cardiogenic shock. **Left,** thallium-201 myocardial perfusion images in anterior **(top)** and left anterior oblique **(bottom)** views. **Center and right:** left anterior oblique end-diastolic and end-systolic gated blood pool images. A perfusion defect is evident in the left anterior oblique thallium-201 image. The gated blood pool images reveal a small left ventricle with only moderately reduced function. The striking finding is a large dilated, poorly contracting right ventricle, suggestive of right ventricular damage.

Cardiogenic Shock

In cardiogenic shock due to acute myocardial infarction, thallium-201 myocardial imaging and gated blood pool scans may also be of value. In most instances, cardiogenic shock is due to massive left ventricular damage. Under these circumstances the thallium-201 image and gated scan reveal a massive perfusion deficit, poor wall motion and a low left ventricular ejection fraction (Fig. 3). In these patients the scanning techniques often merely confirm the poor prognosis. However, the finding of an area of retained myocardial perfusion in the thallium-201 scan and regional myocardial wall motion in a corresponding area of the gated cardiac blood pool scan may be an indication for a more aggressive approach, including intraaortic balloon pumping and coronary bypass graft surgery. In a patient with a diffuse abnormality of regional myocardial perfusion and diffuse left ventricular hypokinesia any therapy may be futile.

Shock due to right ventricular infarction: In some patients with infarction complicated by cardiogenic shock the thallium-201 myocardial perfusion image may show only a relatively small perfusion defect of the left ventricle and the gated cardiac blood pool scan a small and relatively well contracting left ventricle. The striking findings in these patients are massive dilatation and poor contractility of the right ventricle (Fig. 4), suggesting the syndrome of right ventricular infarction.[14] The electrocardiogram frequently shows inferior or true posterior myocardial infarction with second or third degree heart block. Hemodynamic studies with a Swan-Ganz catheter may reveal increased right ventricular filling pressure, equal to or greater than the left. In some patients, however, because of a change in compliance, right ventricular filling pressure may not be abnormally elevated despite the presence of massive right ventricular infarction.[14] In these patients evidence of right ventricular dilatation in a gated cardiac blood pool scan should suggest the syndrome of right ventricular infarction, and plasma volume expansion should be instituted with careful observation of left ventricular filling pressure so as to avoid pulmonary edema. If this condition is recognized early and appropriate therapy instituted, the long-term prognosis is excellent because the left ventricle may not be severely damaged.

Rupture of papillary muscle or ventricular septum: In patients with cardiogenic shock or severe left ventricular failure due to rupture of a papillary muscle or the interventricular septum, myocardial perfusion imaging and gated cardiac blood pool scanning may also be of value. In a patient with a sudden loud systolic murmur and left ventricular dysfunction, injection of technetium-99m albumin through a Swan-Ganz catheter with the patient in the left anterior oblique position allows one to detect the interventricular septal defect at the bedside by simultaneous observation of filling of the right and left ventricles. A ruptured papillary muscle can be suspected in this situation from the absence of a left to right shunt and the finding of an enlarged left atrium. A similar conclusion may be reached in most instances after measurement of left ventricular filling pressures and oxygen saturation levels, but the major factor determining operability and long-term survival in these patients is the extent of left ventricular damage. The finding of a localized defect in the thallium-201 myocardial perfusion image and a well maintained left ventricular ejection fraction in the gated cardiac blood pool scan would therefore suggest a good prognosis and low risk of operative mortality. Early surgery in such patients may be life-saving. In those with extensive left ventricular damage the prognosis is poor even if surgery is delayed several months.

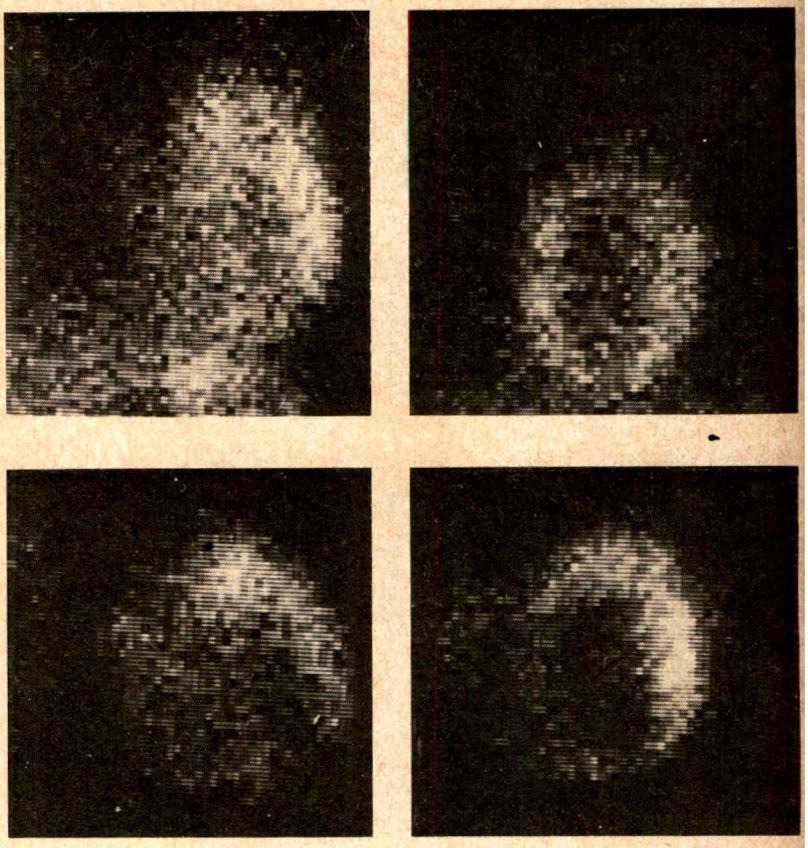


FIGURE 5. Thallium-201 myocardial perfusion images at rest **(top)** and during exercise stress **(bottom)** in a patient with a previous inferior myocardial infarction and significant narrowing of the right and the left anterior descending coronary artery. **Left** images, anterior view; **right** images, left anterior oblique view. A resting defect is evident in the inferior wall (anterior view). In the images obtained during exercise, the inferior defect becomes more pronounced and a new defect appears in the septal region (left anterior oblique view).

Congestive Heart Failure

Congestive heart failure after myocardial infarction presents a problem in patient management. When the failure is due to a localized left ventricular aneurysm, surgical resection may relieve the patient's symptoms and prolong life. When extensive myocardial damage results in diffuse left ventricular hypokinesia, surgery is poorly tolerated and continued medical therapy is indicated. Performance of a gated cardiac blood pool scan[15] and thallium-201 myocardial perfusion imaging allows differentiation of these two conditions on an outpatient basis. If a localized left ventricular aneurysm is detected with good residual myocardial perfusion of the noninfarcted myocardium, hospitalization for coronary arteriography and left ventricular angiography is advised. It is our current practice not to admit patients with diffuse left ventricular hypokinesia and poor residual perfusion to the hospital for angiography because surgery is unlikely to alter prognosis.

Angina Pectoris

Exercise electrocardiography is commonly used to detect myocardial ischemia in patients with suspected ischemic heart disease. However, studies from several centers[16,17] have shown that exercise electrocardiography is relatively insensitive in patients with single vessel disease and in those with a previously abnormal resting electrocardiogram. Myocardial perfusion imaging with thallium-201 at rest and during stress has recently been shown to be more sensitive than exercise electrocardiography in detecting ischemia in patients with proved significant narrowing of a single coronary artery and in those with a previously abnormal resting electrocardiogram.[18]

In patients without significant coronary arterial narrowing any inhomogeneity of thallium-201 uptake in the resting myocardial perfusion image becomes less apparent after exercise.[19] Hepatic and gastric activity are relatively reduced during exercise so that the ratio of myocardial thallium-201 uptake to background is reduced. In patients with significant coronary arterial narrowing a new perfusion defect may appear during exercise (Fig. 5). If the perfusion defect seen after exercise is not present at rest, transient myocardial ischemia can be diagnosed, if the defect persists in the same location as a rest, myocardial infarction is present.

Detection of false positive exercise tests: One of the most important uses of this technique may be in the detection of false positive exercise electrocardiographic tests. Exercise electrocardiographic testing in asymptomatic populations has been found to result in a relatively large percentage of false positive results.[20] A positive exercise thallium-201 myocardial perfusion image in conjunction with a positive exercise test would add weight to the diagnosis of ischemic heart disease. A negative exercise thallium-201 image with a positive electrocardiographic response should raise some doubts as to the diagnosis and suggest further independent

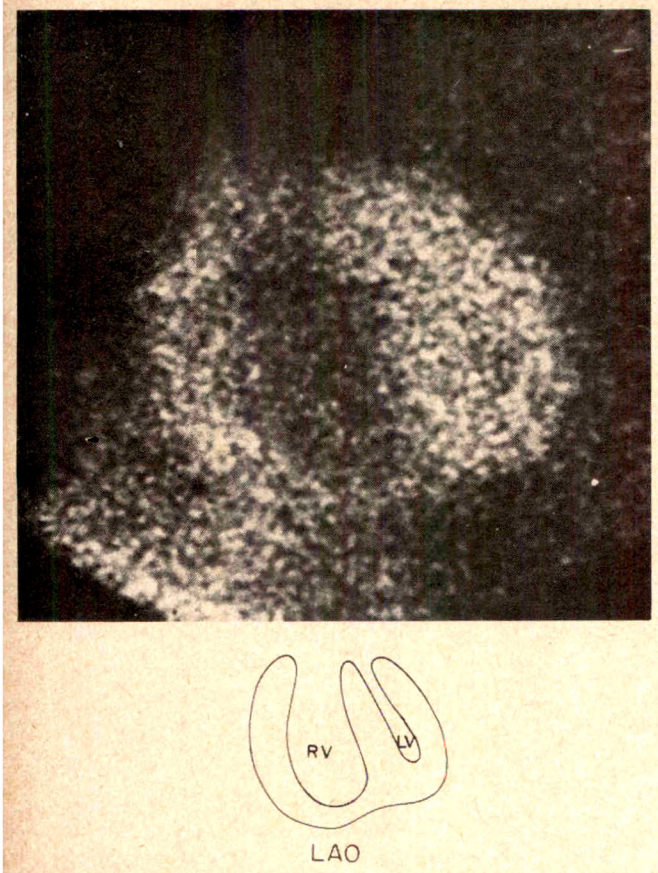


FIGURE 6. Patient with long standing cor pulmonale. **Top,** left anterior oblique thalium-201 myocardial perfusion image; **bottom,** schematic drawing. LV = left ventricular cavity; RV = right ventricular cavity. Note the markedly dilated right ventricular cavity and the appearance of a relatively thickened right ventricular myocardium.

diagnostic studies, possibly including selective coronary arteriography.[21]

Evaluation of patients undergoing coronary bypass surgery: Another area where myocardial imaging is finding increased use is in the evaluation of patients undergoing coronary bypass surgery for symptomatic angina pectoris. As mentioned, an exercise thallium-201 myocardial perfusion image may detect myocardial ischemia in patients whose exercise electrocardiogram remains normal. The appearance of a perfusion defect during exercise suggests that a given coronary arterial narrowing is responsible for the patient's symptoms of myocardial ischemia. The failure to demonstrate an abnormal thallium-201 image or exercise electrocardiogram in a patient with a subcritical coronary arterial narrowing of approximately 50 percent suggests that the lesion may not be hemodynamically significant or that collateral flow is adequate. On the other hand, the absence of thallium-201 uptake at rest in an area of myocardium supplied by a significant coronary arterial narrowing suggests previous myocardial infarction and recannulization of the narrowed vessel. Coronary bypass surgery in such a situation is unlikely to be of benefit. However, in patients with unstable angina pectoris, a relative but not total absence of thallium-201 uptake may indicate reversible ischemia.

If a gated cardiac blood pool scan and a rest and exercise thallium-201 myocardial image are obtained before coronary bypass surgery and repeated postoperatively, it is possible to obtain noninvasively a good estimate of the results of surgery. The appearance of a new perfusion defect or wall motion abnormality postoperatively is diagnostic of intercurrent myocardial infarction. Studies by Cohen et al.[22] suggest that areas of new myocardial damage may be detected with these techniques twice as frequently as from the appearance of Q waves in the electrocardiogram. New myocardial damage may also be detected by the appearance of a positive infarct avid scan with technetium-99m pyrophosphate.[23]

Improvement in myocardial perfusion and graft patency can be diagnosed if a previous perfusion defect during exercise or a resting wall motion abnormality disappears postoperatively. With these noninvasive techniques it should be possible to reduce the need for postoperative angiography.

Nonischemic Cardiomyopathy

Myocardial infiltrative process: The detection of a perfusion defect or abnormality of regional myocardial wall motion at rest, while diagnostic of myocardial damage, does not necessarily indicate ischemic heart disease as the cause. Any infiltrative process such as a tumor, amyloidosis or granulomas may destroy myocardial cells and result in a perfusion defect and wall motion abnormality. Bulkley et al.[24] recently found thallium-201 myocardial perfusion imaging of use in evaluating patients with sarcoidosis. Direct myocardial involvement was detected in several patients in whom the diagnosis would not otherwise have been possible. The finding of direct myocardial involvement by sarcoid granuloma is an indication for steroid therapy. An abnormality in the myocardial perfusion image or gated cardiac blood pool scan is not specific. Clinical circumstances usually allow the proper clinical diagnosis. Another finding of interest in patients with pulmonary sarcoidosis is the presence of right ventricular hypertrophy.

Right ventricular hypertrophy: The detection of right ventricular hypertrophy with myocardial perfusion imaging with thallium-201 appears to be more sensitive than routine electrocardiography especially in patients with concomitant left ventricular hypertrophy.[25] In patients without pulmonary hypertension or other causes of right ventricular hypertrophy, right ventricular thallium-201 activity is barely visible in the left anterior oblique myocardial perfusion image. Thallium-201 activity is present in normal right ventricular myocardium in proportion to blood flow. However, right ventricular myocardium is thinner than the left and may also have a lower flow per gram because of its low oxygen requirements compared to the left. Since the ratio of left ventricular myocardial thallium-201 activity to lung background is in the order of

only 2:1, the contrast settings commonly used to view the left ventricle do not allow adequate definition of the low level of activity in the right ventricular myocardium. To assess the right ventricular myocardium the scan should optimally be viewed at a low contrast setting. When viewed at this setting, the right ventricular myocardium can be seen in most normal patients but is significantly thinner than in patients with right ventricular hypertrophy.

Cohen et al.[25] found that right ventricular hypertrophy could be detected with thallium-201 myocardial perfusion imaging more reliably than with routine electrocardiography especially in patients with concomitant left ventricular hypertrophy in whom the electrocardiographic diagnosis of right ventricular hypertrophy is especially difficult. Patients with long-standing pulmonary hypertension were found to have a right ventricle of greater than 1 cm of thickness on the ungated left anterior oblique thallium-201 scan (Fig. 6). In some patients, the right ventricular chamber was dilated and hypertrophy was present so that the left anterior oblique scan suggested the Greek letter omega. The thallium scan can be used to assess the relative thickness of both the right and left ventricular myocardium. This should prove of value in the detection and follow-up of patients with pulmonary or systemic hypertension. However the thickness measurements obtained from the ungated thallium-201 myocardial perfusion scan are greater than those actually present, because of heart motion. Triggering the scintillation camera to obtain end-diastolic images would more closely reflect true wall thickness, but the time required to obtain an end-diastolic image of sufficient quality is approximately 30 minutes, which in most circumstances is impractical.

Myocardial Thickness (Asymmetric Septal Hypertrophy)

Assessment of relative myocardial thickness from the resting thallium-201 myocardial perfusion image is also of value in patients with suspected asymmetric septal hypertrophy.[26] In normal subjects the thickness of the interventricular septum is approximately equal to the thickness of the lateral wall of the left ventricle. The relative thickness of these structures can easily be assessed from the left anterior oblique thallium-201 myocardial perfusion image (Fig. 7). In patients with concentric left ventricular hypertrophy due to systemic hypertension or aortic stenosis the ventricle thickens, but the ratio of septal to left ventricular free wall thickness, remains normal.[26] Most patients with idiopathic hypertrophic subaortic stenosis have asymmetric hypertrophy of the interventricular septum and an increased ratio of septal to lateral free wall thickness. Echocardiography is the procedure most often used to demonstrate asymmetric septal hypertrophy. However, in some patients it may not be possible to obtain a technically satisfactory echocardiogram, owing to an increased anterior-posterior diameter of the chest and overlying lung, whereas in others, the asymmetric septal hypertrophy detected with echocardiography may be secondary to right ventricular hypertrophy rather than idiopathic hypertrophic subaortic stenosis.

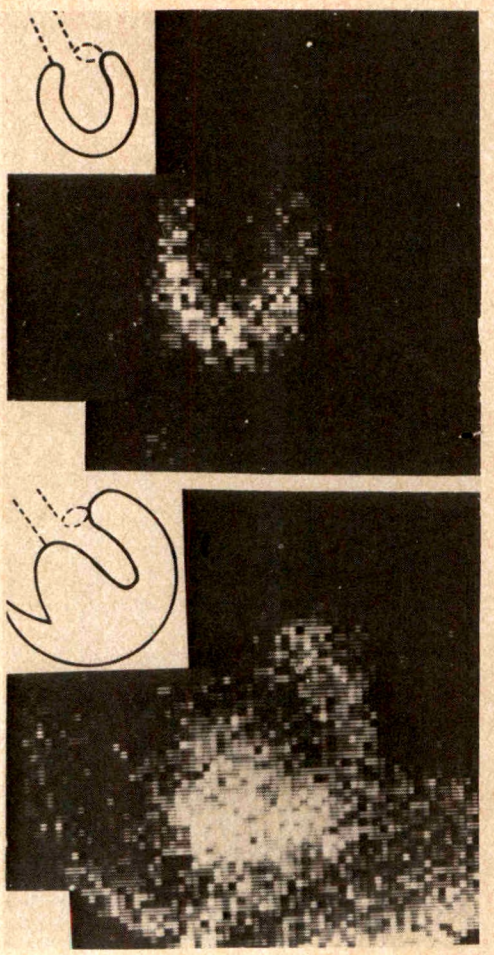


FIGURE 7. Comparison of left anterior oblique thallium-201 myocardial perfusion images in a normal patient **(top)** and a patient with idiopathic hypertrophic subaortic stenosis with asymmetric septal hypertrophy **(bottom).** Note the relatively equal thickness of the septal and lateral walls in the normal image. In the patient with idiopathic hypertrophic subaortic stenosis there is a relatively thickened septal region in comparison with the lateral wall. (Reprinted from Bulkley et al.[26] with permission.)

Cardiomyopathy (Ischemic versus Nonischemic)

In a patient with an enlarged heart and symptoms suggestive of a cardiomyopathy, thallium-201 myocardial perfusion imaging may allow differentiation of an ischemic from a nonischemic cardiomyopathy. The resting gated cardiac blood pool scan may show an enlarged diffusely hypokinetic left ventricle in both situations. In patients with an ischemic cardiomyopathy, the thallium-201 myocardial perfusion image will show almost absent or spotty tracer uptake whereas in patients with a primary nonischemic cardiomyopathy, myocardial perfusion and tracer thallium-201 uptake may be uniform or only slightly inhomogeneous. The finding of uniform thallium-201 uptake in such patients would strongly suggest a nonischemic cardiomyopa-

thy.[27] The finding of a patchy uptake or a perfusion defect, although suggestive of ischemic cardiomyopathy, can be due, as pointed out earlier, to secondary myocardial infiltration.

Clinical Implications

The application of myocardial imaging to clinical cardiology holds great promise for better noninvasive assessment of cardiac disease. With the development of new radiopharmaceutical agents and improved instrument resolution, clinical application of these techniques will increase. It should be possible to monitor the distribution in the body of pharmacologic agents, determine specific metabolic functions such as fatty acid utilization, as well as provide more quantitative information concerning myocardial perfusion, infarct size and left ventricular function.

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The Nuclear Stethoscope: A Simple Device for Generation of Left Ventricular Volume Curves

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Initial evaluation has begun of a system for displaying left ventricular time-activity curves, relating the intraventricular content of radioactivity with the cardiac cycle as determined by the patient's electrocardiogram. Major problems include proper positioning of the detector, correction for background radioactivity outside the ventricle and calibration of the device to permit conversion of measurement of radioactivity to measurement of ventricular volumes.

One of the most important advances in the diagnosis of cardiovascular disease is the use of radioactive tracers to measure regional myocardial perfusion and the motion of the ventricular walls in coronary and other types of heart disease. Valuable as these studies are proving to be, they suffer from one major drawback: the expense of the equipment required. To perform such a study with the scintillation camera and its associated data processing requires more than $100,000 worth of equipment, and the study ordinarily takes up to 1 hour to perform.

To make certain of these studies more readily available—for example, for monitoring a group of patients in a coronary care unit—we have designed, constructed and carried out initial clinical evaluation of a simple device called a "nuclear stethoscope," that we hope will bring some of the potential uses of cardiovascular nuclear medicine to small medical centers and hospitals and possibly some day even to the physician's office (Fig. 1). The device is compact and inexpensive because it dispenses with spatial resolution. In other words, it does not produce images of the heart but portrays a time-dependent image of the rate of filling and emptying of the left ventricle as a whole.

Method

The patient is given an injection of technetium-99m albumin, which becomes distributed rapidly throughout the heart and blood vessels. The amount of tracer within the heart is measured by a simple crystal scintillation detector, small enough to be held by hand against the patient's chest as the heart fills and empties. The detector must be positioned so that radioactivity within the ventricle is being detected although activity from other sources surrounding the ventricles must be taken into account. This is referred to as background activity. The crystal detector is attached by way of intermediate electronic equipment to a recording device that displays the activity being viewed by the detector in relation to the patient's electrocardiogram. The device is designed to divide the interval between successive R waves into 48, 96 or 192 intervals or "time slots." For each of these intervals, the heart's content of radioactive tracer is measured and depicted on a television screen in the form of a developing left ventricular time-activity curve.

The image of the left ventricular time-activity curve is produced by displaying simultaneously on a television screen the activity in 48 to 192 memory channels beginning at the time of the patient's electrocardiographic R wave. The parallel lines of the television raster correspond to memory channels. The count rate stored in a particular memory channel causes the video signal for the corresponding raster line to be maintained at a binary level for a corresponding time interval. This produces a bar graph in which the length of each bar indicates the

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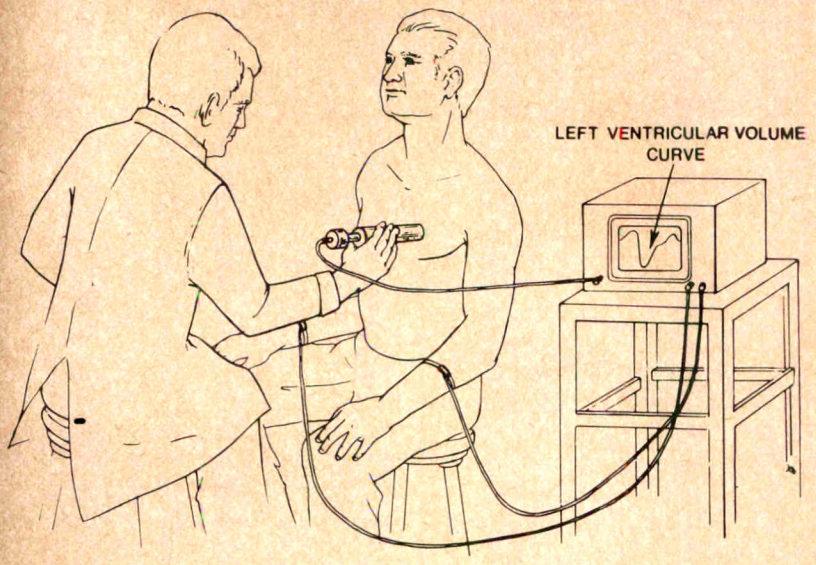


FIGURE 1. Illustration of the principle of the nuclear stethoscope. The electrocardiographic leads provide the pulses for dividing ventricular radioactivity into the proper time slots after the QRS complex.

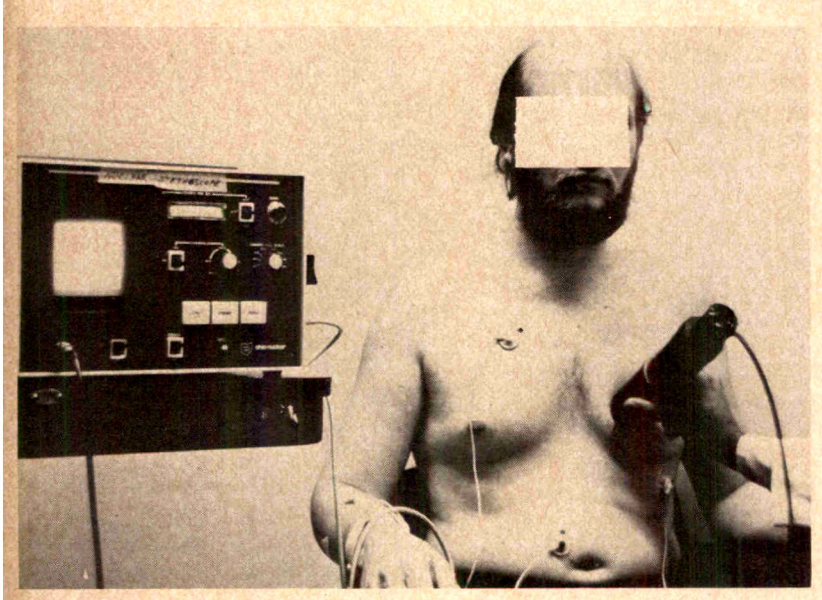


FIGURE 2. Photograph of the prototype.

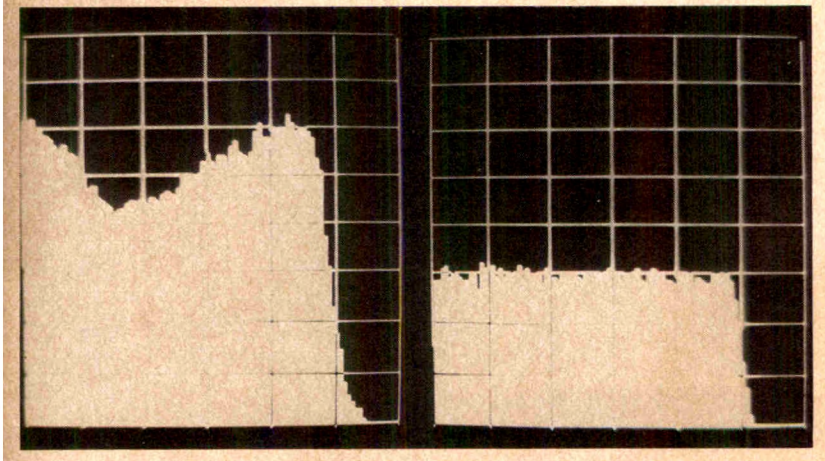


FIGURE 3. Left ventricular time-activity curve on the left, background activity on the right. The **vertical axis** is activity; the **horizontal axis** is time after the QRS complex.

amount of radioactivity being seen by the radiation detector during the corresponding time of the cardiac cycle. As each memory channel accumulates radioactivity count rates during several hundred cardiac cycles, each bar lengthens to indicate the cumulative increase in activity during each time slot until an interpretable left ventricular time-activity curve is obtained.

The prototype device: In the first version of the device, a crystal scintillation detector, 2.54 cm in diameter, was combined with parallel hole lead collimators 2.54 cm in length and 0.95 to 1.27 cm in diameter (Fig. 2). The detector was placed over the chest wall at a point medial to the point of maximal cardiac impulse with the axis of the detector in a manner similar to the left anterior oblique angiographic view.

The radioactive tracer in the blood produces output pulses that are counted and stored over brief repeating intervals of time in a multichannel memory. The first channel of memory is gated by detection of the QRS complex in the patient's electrocardiogram, the recording of which is an intrinsic part of the device. Thereafter, the channels of memory are successively addressed so that each successive radioactivity count rate over repeating time intervals is stored in corresponding memory channels. With each successive heartbeat, the process is repeated and new counts are added to the counts already in storage in a particular channel.

While the count rates are being recorded, the memory channels are read out to a television type display in which each memory channel is correlated with a horizontal line sweep. At the beginning of each line, the video input signal is switched from a low level to a high level where it remains for a period of time that corresponds to the accumulated total in the memory channels, thus writing solely on the television screen whose length is determined by the progressively accumulated radioactivity counts.

Since successive lines of the television display correspond to the different intervals of the cardiac cycle, the physician can observe the progressive build-up of an image over a period of about 1 minute that reflects the rising and falling of the amount of the tracer within the field of view of the detector (Fig. 3). If the detector is positioned properly, the curve will correspond to the left ventricular time-activity curve. With proper calibration to permit conversion of the amount of radioactivity to the amount of blood in cubic centimeters, the left ventricular volume curve can be obtained.

The device is also designed to record the time course of the tracer as it passes through the heart after the initial intravenous injection. On the basis of these results with the prototype, the design has been modified and a new device is under construction.

The left ventricular time-activity curve: In Figure 3, the vertical axis displays accumulated counts in each time interval after the QRS complex corresponding to the zero intercept on the horizontal axis. Each bar corresponds to a time interval after the QRS complex. In this case full scale on the horizontal axis is approximately 1 second. The video screen displays the updated contents of all the time intervals at once. The X axis

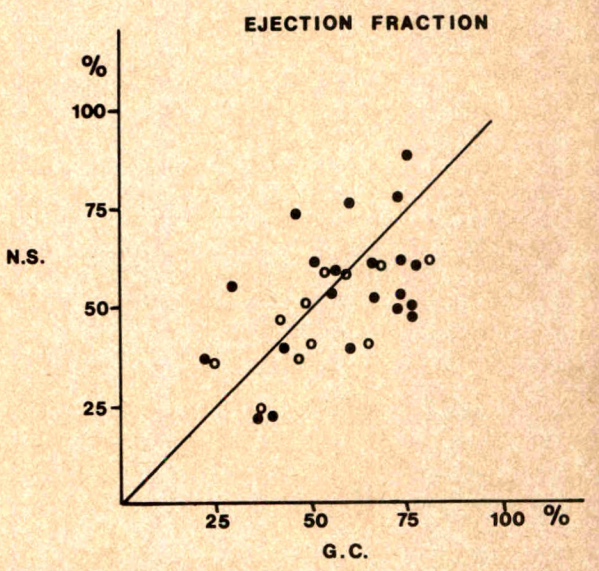


FIGURE 4. Relation between ejection fraction measured with the nuclear stethoscope (N.S.) **(vertical axis)** and with the scintillation camera (G.C.) method of measuring ventricular dimensions in 44 patients. The **open** and **closed circles** represent data measured by two different investigators.

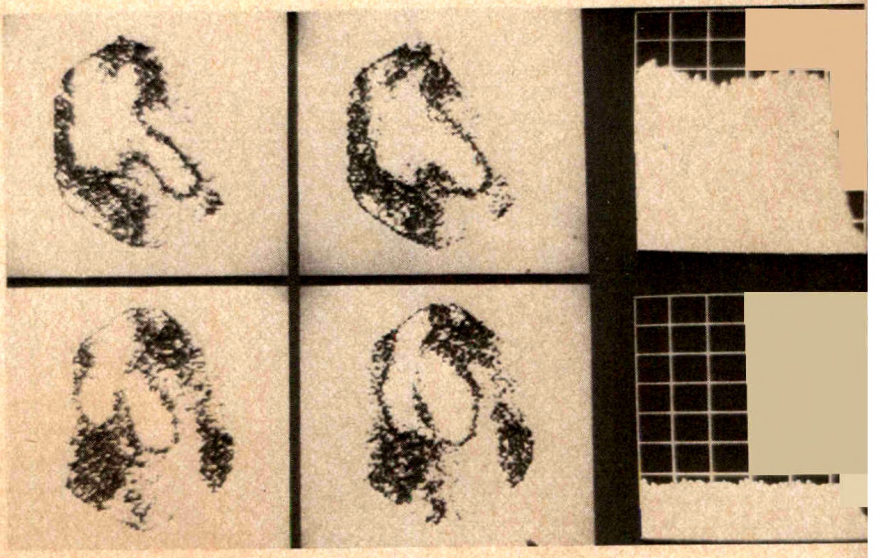


FIGURE 5. Gated scintillation camera images are compared with a left ventricular volume curve obtained in the same patient. Images in **left panels,** systolic frames; images in **center panels,** diastolic frames. **Upper right** panel shows volume curve measured by coupling the output of a scintillation camera to the nuclear stethoscope. **Lower right** panel shows background activity associated with the volume curve.

represents time and the Y axis represents radioactivity. The full extent of the X axis corresponds to an average conglomerate cardiac cycle; the displayed curve represents the variation in radioactivity during repetitive cardiac cycles. The image builds up, one cardiac cycle after the other, until the physician has obtained the required information. The right panel of Figure 3 shows background activity obtained by positioning the detector over the left lung away from the heart.

In use, the portable instrument is brought to the patient's bedside, and the patient is given an injection of ^{99m}Tc-labeled human serum albumin in a dose of 1 to 20 mCi. About 10 minutes after injection, the physician or technologist places the detector over the patient's precordium and, observing the count ratemeter while positioning the detector in the estimated left anterior oblique angiographic position, locates the point of maximal radioactivity. Then, the image is observed for about 30 seconds with minor changes in the position of the detector until the maximal stroke volume is observed, that is, the point when the difference between maximal activity corresponding to end-diastole and minimal activity corresponding to end-systole is greatest. Care is taken to avoid the left atrium.

After the left ventricular curve has been obtained, the detector is moved to the left to obtain the background activity (Fig. 3). The detector is moved to the left until the rise and fall of radioactivity in relation to the electrocardiogram is no longer observed. The period of observation of background and of left ventricular activity must be identical so that the former can be subtracted from the latter.

Results

The normal left ventricular time-activity curve: In normal persons at rest, the left ventricular time-activity curve is usually similar to that in Figure 3. Immediately after the QRS complex, the preejection period is evident; the ventricle has begun contracting, but the aortic valve has not opened and the left ventricle has not yet begun to empty. When the intraventricular pressure increases sufficiently to open the aortic valve against the pressure within the aorta, the activity level recorded by the detector falls as blood flows out of the heart and levels off after the aortic valve closes. It begins rising again as the heart refills. When filling is completed, there is another flat region in the curve, the isovolumetric diastolic period, or diastasis, before contraction of the ventricular muscle starts another cycle. In the normal resting person, the intraventricular volume is level for about one third of the cardiac cycle. With exercise, the isovolumetric diastolic period diminishes or disappears completely.

The maximal activity corresponds to end-diastolic volume, whereas the low point of activity corresponds to end-systolic volume; after background activity has been subtracted, subtracting end-systolic from end-diastolic volume gives stroke volume which, divided by the diastolic volume, gives ejection fraction. Stroke volume averaged over 30 seconds to 1 minute gives cardiac output.

Comparison with other methods: Currently we are comparing the results obtained with the nuclear stethoscope with those obtained in the same patients with nuclear imaging studies, echocardiography and, in some cases, contrast angiography. The correlation of the ejection fraction measured in 44 patients with the scintillation camera and the nuclear stethoscope is shown in Figure 4. The camera method consisted of measuring the ventricular dimensions from camera images and the use of the Dodge, Sandler formulas for calculation of end-systolic and end-diastolic volumes.

These studies should give a clearer idea of what the still experimental nuclear stethoscope can and cannot do. We intend to see how closely specific abnormalities in the ventricular volume curves correlate with anatomic or pathologic abnormalities revealed by other methods.

Discussion

Clinical implication: It is too early to evaluate the diagnostic potential of the nuclear stethoscope in relation to the more elaborate cardiovascular nuclear medicine procedures where diagnostic value seems already well established. It is likely that the device may find its greatest use in association with the scintillation camera, which can be used as a detector to achieve more precise localization of the left ventricle (Fig. 5). Particularly in patient monitoring, one or more nuclear stethoscopes may be able to provide the cardiologist with rapid feedback on the effect of a given regimen, such as digitalis or counterpulsation. It may also help in quantifying the effects of exercise in the recovery period after myocardial infarction, and possibly, in adjusting the dose of medications for maximal benefit to the ventricular function of the individual patient.

Future directions: Problems still requiring investigation are the size and configuration of the collimator, the rules that should be followed to ensure correct positioning of the detector, the correction required for background activity, and the accuracy of the device in measuring preejection period, left ventricular ejection time, the rates of emptying and filling of the ventricle, end-systolic and end-diastolic volumes and ejection fraction. At present, it seems that it is most accurate in measurement of time intervals, moderately accurate in measurement of ejection fraction and least accurate in measuring absolute volumes because of problems with calibration of activity to yield volumes and problems of correcting for background.

Reference

1. **Wagner HN Jr, Natarajan TK, Strauss HW, et al:** The nuclear stethoscope: a bedside device for continuous monitoring of ventricular function (abstr). Circulation 52: Suppl II: II-70, 1975

Pathophysiologic Studies of the Pulmonary and Coronary Circulations in Man

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Studies of the pulmonary circulation in normal man, performed with external radiation detectors, have shown that pulmonary blood volume is about 10 percent of total blood volume. Pulmonary blood volume was unchanged in patients with acute or chronic left atrial hypertension and in normal persons during expansion of total blood volume in spite of marked increases in pulmonary vascular pressures. However, pulmonary blood volume was greatly increased in patients with polycythemia rubra vera and a large total blood volume and in patients with a left to right shunt but normal pulmonary intravascular pressure.

Studies of regional myocardial perfusion with injection of xenon-133 solution into the left coronary artery revealed localized areas of ischemia distal to stenotic lesions even when the patient was at rest. During angina produced by pacing, more severe ischemia occurred, thus suggesting that functional factors reduce local perfusion below resting levels.

In patients with "variant" angina, intravenous injection of thallium-201 chloride during spontaneous attacks has revealed large cold areas in myocardial scintigrams not present under control conditions, thus suggesting severe transmural reduction of perfusion in heart muscle corresponding to S-T segment elevation in the electrocardiogram.

The ability to measure the distribution of radioactive tracers within the body by means of external radiation detection makes these tracers ideal indicators in noninvasive investigations of the heart and circulation. The progressive development of tracers with suitable physical and biologic characteristics and the continuous improvement of the detecting instruments have made such studies routine in many nuclear medicine departments. Procedures have been devised for cardiovascular screening as well as for more definitive diagnostic tests, as described elsewhere in this Symposium.

This report is concerned with the use of radioactive tracers during invasive cardiac investigations in both hemodynamic laboratories and intensive care units. I have tried to provide some examples of the results of a continuing program in which nuclear medicine and traditional hemodynamic techniques are combined in a cardiovascular department. Data on the pulmonary circulation, most of which have already been published, are mentioned, and results of a series of recent investigations on myocardial perfusion, mostly unpublished, are described.

Studies of the Pulmonary Circulation

After experimental validation of the radiocardiographic technique proposed by Donato et al.[1] for measurement of cardiac output[2,3] and of the method proposed by Giuntini et al.[4] for measurement of pulmonary blood volume,[5] these procedures have been used routinely in our cardiac catheterization laboratories and intensive coronary care unit. In par-

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ticular, measurements of pulmonary blood volume with the use of a single precordial probe after right atrial injection of radioiodinated human serum albumin (^{131}IRIHSA) have made it possible to obtain these data in normal subjects and patients in whom left atrial catheterization is not justified.[6–10]

Studies in the cardiac catheterization laboratory: *In normal subjects* we have been able to define the normal value of pulmonary blood volume, which in different series[4,11–13] averages about 300 ml/m^2 of body surface area or about 10 percent of total blood volume. We have also established that stroke volume is the hemodynamic variable most closely correlated with pulmonary blood volume under a variety of hemodynamic conditions,[14] thus suggesting that the kinetic energy of the stroke volume may play a significant role in the recruitment of vascular units in the pulmonary circulation.[15] By contrast, simultaneous measurements of pulmonary intravascular pressures and pulmonary blood volume in persons with no cardiovascular disease have revealed that the normal pulmonary circulation has a rather small level of compliance[13] and responds to a rapid increase of left atrial pressure produced by blood volume expansion with a diffuse increase of vascular or perivascular smooth muscle tone.[13] On the other hand, a 50 percent increase of total blood volume observed in five patients with polycythemia rubra vera and normal pulmonary intravascular pressures was accompanied by a 40 percent increase in pulmonary blood volume, thereby indicating that the pulmonary vascular bed can accommodate larger amounts of blood without an increase in vascular or perivascular smooth muscle tone.[16]

In patients with chronic pulmonary venous hypertension secondary to acquired disease of the left side of the heart, we have confirmed that average pulmonary blood volume is within normal limits in spite of the large increase in intravascular pulmonary pressure[17,18]; this finding is in agreement with data obtained by double injection into the pulmonary artery and left atrium.[6–8] Repeat measurements following reparative cardiac surgery have shown that pulmonary blood volume increases in patients whose hemodynamic improvement is accompanied by a reduction of pulmonary intravascular pressures.[19]

In patients with an atrial septal defect and a 2:1 left to right shunt, pulmonary blood volume is 50 percent greater than normal, the increase being roughly in proportion to the increase in right ventricular stroke volume.[20] This finding supports the hypothesis that, in the absence of structural changes, stroke volume is one of the most important determinants of pulmonary blood volume.[19]

Studies in the coronary care unit: Acute myocardial infarction is accompanied by left ventricular dysfunction, acute increases in left atrial and pulmonary pressures and clinical and radiologic signs of "pulmonary venous congestion." The sudden onset of pulmonary venous hypertension in left ventricular dysfunction represents a basically different situation from that encountered in valve disease of the left side of the heart because it allows little time for adaptation of the pulmonary vasculature. Measurement of pulmonary blood volume in patients during the acute phase of infarction and after subsequent recovery indicated that the large increase in pulmonary intravascular pressures was not accompanied by a significant increase in pulmonary blood volume.[22,23] During recovery, reduction of pulmonary intravascular pressures was not accompanied by consistent changes in pulmonary blood volume (Fig. 1). Thus, the radiologic finding of "acute pulmonary venous congestion" is due to interstitial accumulation of fluid, as indicated by recent determinations of extravascular lung water.[24]

These observations confirm that pulmonary blood volume is controlled only to a small extent by left atrial pressure whether it is increased acutely by volume expansion[13] or by left ventricular failure.[22,23] Although one cannot exclude the possibility that mechanisms secondary to an increase in left atrial pressure may tend to oppose the expansion of pulmonary blood volume resulting from increased transmural pressures, pulmonary blood volume in man appears to be controlled chiefly by stroke volume[18] and in dogs by inflow pressure or flow.[15] These mechanisms appear to be mainly related to the recruitment of vascular units.[15]

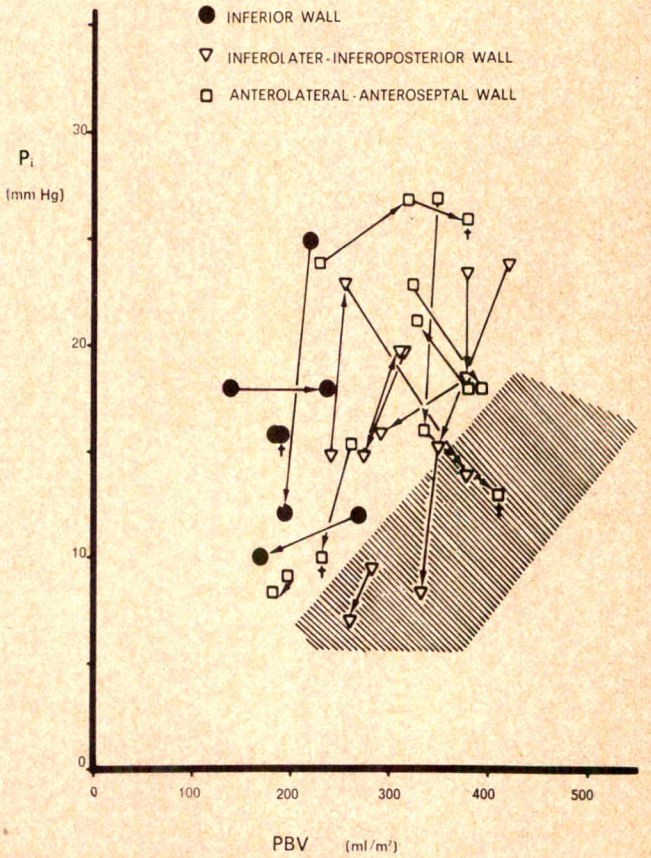


FIGURE 1. Values for pulmonary blood volume (PBV) during the 1st week after acute myocardial infarction plotted against the corresponding values for pulmonary mean intravascular pressure. Pi = pulmonary arterial plus pulmonary wedge pressure divided by 2. The **shaded zone** indicates the normal relation between the two values.

Studies of the Coronary Circulation

The use of radioactive tracers in the study of the coronary circulation has been called a "new approach to coronary heart disease."[25] The correct application of these tracers and the proper interpretation of procedures, such as those designed to measure myocardial perfusion, must be based on an understanding of the pathophysiologic events that occur. One must be aware of both the limitations and the advantages of the new techniques.

In spite of the large body of data obtained in experimental animals and the large number of measurements of myocardial blood flow in patients, current understanding of the pathophysiology of the coronary circulation in patients with coronary heart disease is still mainly based on traditional assumptions and ideas. In trying to understand the methodologic problems involved in the study of myocardial perfusion, I believe that some knowledge has been gained of the pathophysiologic changes in myocardial perfusion in patients with coronary heart disease.

External counting techniques for measuring myocardial blood flow: Many of the current methods for measuring myocardial blood flow with radioactive tracers are based on the fractionation principle of Sapirstein[26] or on the recording of myocardial washout rates of diffusible indicators injected into a coronary artery.

According to the Saperstein fractionation principle, the fraction of an indicator, uniformly mixed with blood at the left ventricular outlet, distributed to the myocardium during the first circulation equals the fraction of cardiac output that perfuses cardiac muscle. This applies both to particulate indicators that do not recirculate[27] and to recirculating indicators with high extraction rates during the first circulation, such as potassium and other cationic tracers, as long as the amount of nonextracted indicator leaving the myocardium is exactly balanced by the amount that reenters the coronary arteries with recirculation.[28] Under these conditions, when the fraction of the indicator in the myocardium can be measured as a fraction of the injectate, one can calculate total myocardial blood flow (or the fraction of cardiac output that perfuses the myocardium).

According to the "washout principle," one can calculate myocardial blood flow per unit mass of myocardium (or per 100 g) when the mean washout time of the indicator can be determined, the space of distribution of the indicator is confined to the myocardium and its tissue/blood partition coefficient is known.[29]

In applying these methods to clinical practice, often a number of these conditions are not adequately met, or the data are not adequately verified, so that the interpretation of the findings is complex and only a qualitative conclusion is warranted. We have used the method based on the intracoronary injection of a diffusible indicator during studies in the catheterization laboratory and the noninvasive potassium tracer method in our coronary care unit studies.

Coronary vascular reserve: After the initial reports of the single precordial detector method for estimating myocardial blood flow[30,31] and after its validation in animals,[32] we attempted to study the relation between the degree of coronary stenosis observed at arteriography and the ability of myocardial blood flow to increase in response to a stress test (atrial pacing). We used a single precordial detector to obtain the initial myocardial washout slope after left intracoronary injection of solutions of krypton-85 or xenon-133 at rest and during two levels of pacing.[33] Our initial results, like those of others,[34] revealed the practical limitations of the method, which stem from (1) inadequacy of the initial slope for the calculation of the mean washout time in the presence of severe inhomogeneities of myocardial perfusion encountered in coronary heart disease during ischemia[35]; (2) the effects of cardiac fat in determining the washout of these indicators, especially xenon[36,37]; (3) the contribution of recirculating indicator[38,39]; and (4) differences in counting geometry for different parts of the heart. In particular, factors 2 and 3 prevent the use of the stochastic analysis of the washout curve (as opposed to the initial monoexponential extrapolation) in calculating the mean time of washout.

Our initial experience led us to two sets of conclusions, one pathophysiologic and one methodologic:

1. Although we did not consider the calculation of myocardial blood flow/100 g from initial washout curves warranted, we compared the washout slopes at rest and during pacing in different subsets of patients. We assumed that the results were not biased by differences in recirculation or epicardial fat and that initial washout slopes reflected predominantly the washout from better perfused muscle. We observed that the washout rate was slower and increased less in patients with severe stenotic lesions of the coronary vessels than in normal subjects; furthermore, for comparable degrees of coronary stenosis, initial rates were significantly slower at rest and during pacing in patients with signs of left ventricular failure. The values of the washout slope observed in patients with severe coronary heart disease and signs of left ventricular failure were similar to those of patients with left ventricular failure from primary myocardial disease and normal coronary angiograms at comparable heart rates.

These findings are in agreement with data from other reports of patients with triple vessel coronary artery disease[40] and primary myocardial disease.[41] We suggest that changes in left ventricular function rather than the presence of extensive coronary obstruction, as such, may result in lower myocardial blood flow with more effective oxygen utilization per gram of myocardium for a given load.[33] This possibility deserves further study because it is conceivable that in patients with critical coronary obstruction, failure of this adaptive mechanism may lead to an acute imbalance between demand and supply and hence to acute ischemia.

2. Given the wide variability of the factors controlling myocardial oxygen demand[42] and hence the wide range of myocardial blood flow observed even in normal persons,[35] the basic question in patients with coronary artery disease is less "What is the level of myocardial blood flow?" than "Is the level of myocardial blood flow adequate to meet local demands in the various regions of the heart?" Thus, because of the focal nature of coronary artery disease, it may be quite helpful to evaluate perfusion defects on a regional basis. Ischemia in one

area may be offset by increased flow to healthy areas, resulting in normal average or total myocardial blood flow.

Regional myocardial blood flow in relation to coronary stenosis: Imaging the distribution of radioactive tracers within the myocardium allows the detection of the spatial distribution of myocardial blood flow, based on the two principles discussed earlier. Its exact quantitation presents difficulties.

For our studies we used xenon-133, the only diffusible indicator with gamma photon emissions suitable for the gamma camera available to us.[43] On the basis of our previous experience with the single nonimaging detector, we did not base our evaluation of regional flow only on the initial washout slopes, as have other investigators,[44,45] but took the following factors into consideration: (1) areas of xenon-133 retained in epicardial fat (observable in scintigrams obtained 15 minutes after injection); (2) the tail of the washout curves after 90 percent of the injectate had been cleared, in order to detect localized ischemic zones; and (3) the initial distribution of the indicator which, if primarily flow-dependent, might provide information on the regional redistribution of flow to the various zones of the myocardium under different hemodynamic conditions in the same patient.[46]

Under these conditions, constancy of the geometric conditions is a prerequisite, both for the interpretation of changes of regional washout slopes and for the calculation of the fractional initial distribution of xenon to different areas of the myocardium. Using a gamma camera (Nuclear Chicago Pho Gamma III HP) interfaced to a computer (Hewlett-Packard 2116 B),[47] we were able to check the constancy of counting geometry during the course of the washout curves with use of a dual counting device that allowed us to monitor a constant reference indicator (technetium-99m human albumin microspheres injected into the left coronary artery at the beginning of the study). A computer program identified nine areas of interest and for each area provided: (1) the initial fractional distribution of xenon; (2) time-activity curves during the washout of 90 percent of the injected dose; (3) the initial slope of the curve down to 50 percent of the peak (as an indication of the washout in the better perfused myocardium in each area); (4) the percent of the peak activity at which the curve deviated from a monoexponential washout (as an indication of nonhomogeneous washout in each area); (5) the regional residual activity when 90 percent of the injectate was washed out (as an indication of slow washout areas); and (6) the regional xenon distribution 15 minutes after the injection (indicative of the epicardial fat distribution and helpful for the interpretation of the slow washout areas) (Fig. 2 and 3).

In consideration of the limited spatial resolution of the gamma camera and of the blurring caused by heart motion, we studied a group of patients selected according to the following criteria: (1) a long main stem left coronary artery (to ensure adequate mixing of the indicator at the injection site); (2) presence of an isolated critical stenosis in one of the three main left coronary branches but without detectable lesions in the anterior descending or circumflex branches (so that in each patient, in the left anterior projection, the behavior of the tracer in a large myocardial territory distal to the stenosed vessel could be compared with that observed in a large control territory perfused by normal vessels); and (3) typical ischemic electrocardiographic changes during a stress test.

At rest, perfusion in the areas distal to stenosed vessels was characterized by a greater residual activity than in normally perfused areas (+30 percent on the average) at the time when 90 percent of the injected traces was washed out. By contrast, although significant regional differences in initial washout slopes among the different areas were observed, as previously reported,[48] they could rarely be related to the location of the stenosis. For some areas the slower washout could be attributed to a greater xenon-133 retention in fat; for others the differences, which significantly exceeded the error of the estimate, are most likely due to the heterogeneity of myocardial perfusion observed in dogs at

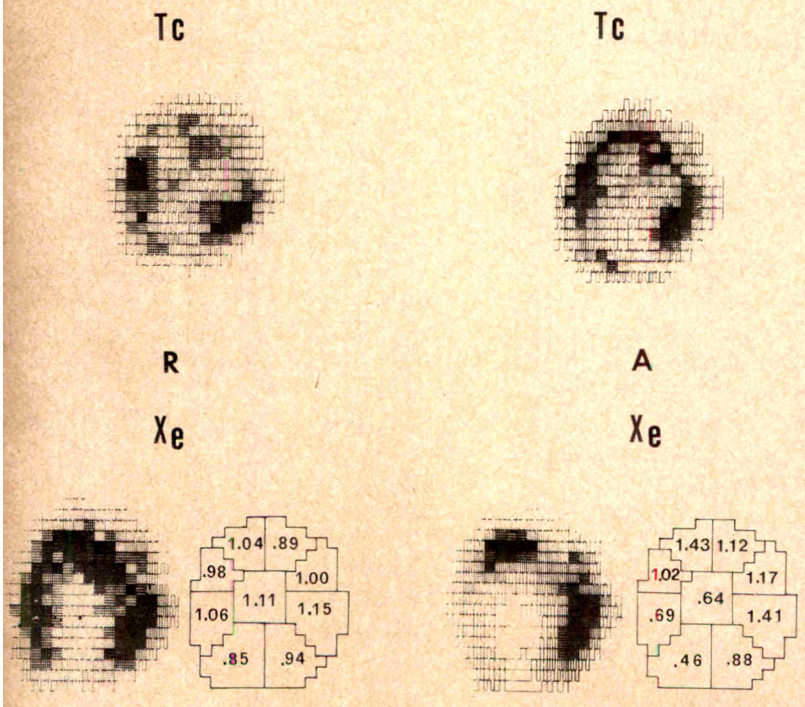


FIGURE 2. Myocardial scintigrams in the left anterior oblique position in a patient who had typical angina but no previous infarction and proximal subtotal occlusion of the left anterior descending coronary artery as the only coronary abnormality. The xenon-133 left coronary scintigram **(lower right)** obtained during pacing-induced angina (A) differs from the scintigram at **lower left** obtained at rest (R), because of the appearance of a large cold area in the territory of the left anterior descending coronary artery. The scintigrams of technetium-99m microspheres (injected into the left coronary artery at the beginning of the study) recorded simultaneously with the two xenon-133 scintigrams are practically unchanged **(upper panels).** The changes in the fractional distribution of xenon per matrix element in each area are indicated in the **lower panels.**

different times.[49] These findings suggest that during rest, sometimes in the presence of a normal electrocardiogram, localized zones of myocardial ischemia may be present distal to a severe coronary arterial obstruction. These zones involve only a fraction of the myocardium included in the areas of interest selected by the computer, probably in the subendocardium, receive little indicator and therefore do not contribute appreciably to initial washout slopes.[50]

During angina induced by atrial pacing, the differences in residual activity became much larger than at rest distal to stenotic vessels relative to control zones in all patients (85 percent difference on the average). Small but consistent differences appeared in the initial washout slopes in most patients, with a slower initial washout beyond the obstructed vessel suggesting that the ischemic zone became larger. However, the differences in the regional initial fractional distribution of the

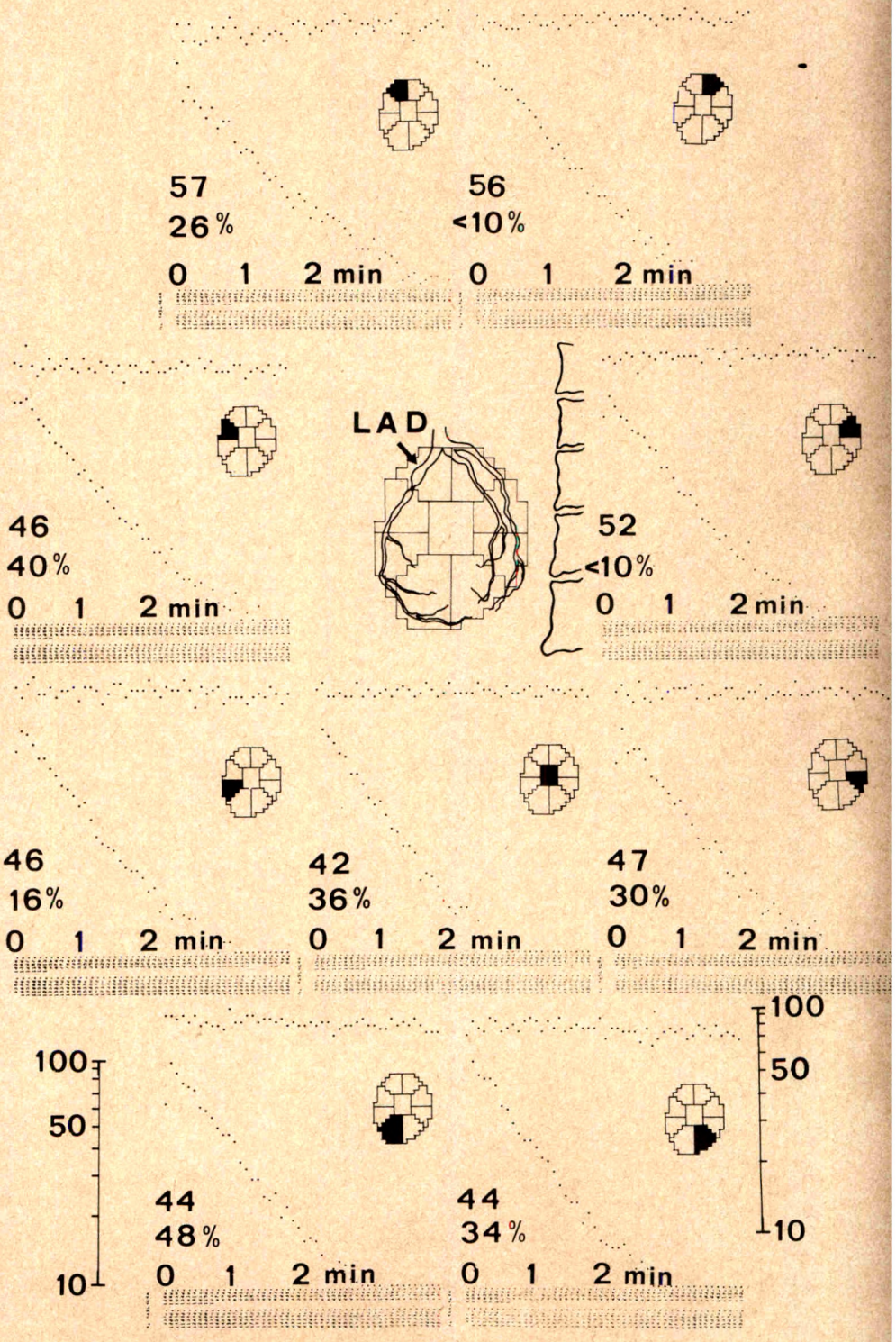


FIGURE 3. Computer plots of the technetium-99m microspheres time-activity curves and of the initial 90 percent washout curves of xenon-133 on a semilogarithmic scale for the various areas **(in black)** into which the scintigram was subdivided in a patient with critical stenosis of the left anterior descending coronary artery (LAD) at rest. Each point represents a 5 second interval. Constancy of counting geometry is indicated by the absence of variation in technetium-99m activity. The half-time of the initial slope and the percent of the peak at which the washout deviates from the initial monoexponential curve are reported for each area.

ndicator (Fig. 3), similar to those observed by others[51] with potassium-43, were much larger than expected on the basis of the changes observed in the initial washout slopes, suggesting that perfusion to the ischemic areas was markedly nonhomogeneous, with some parts of the myocardium receiving too little of the xenon-133 indicator to contribute appreciably to the initial washout curve. This hypothesis was confirmed by inducing angina a second time during the course of the washout after a second injection of xenon, performed during rest. In the patients in whom this was possible, the rate of washout increased in the myocardium perfused by normal vessels but decreased in the ischemic areas (Fig. 4). This finding indicates that in poststenotic areas, perfusion did not increase appropriately to meet local metabolic demands and, in fact, was impaired after pacing induced angina.[50] This observation is important because it is possible that, in a vicious cycle, this func-

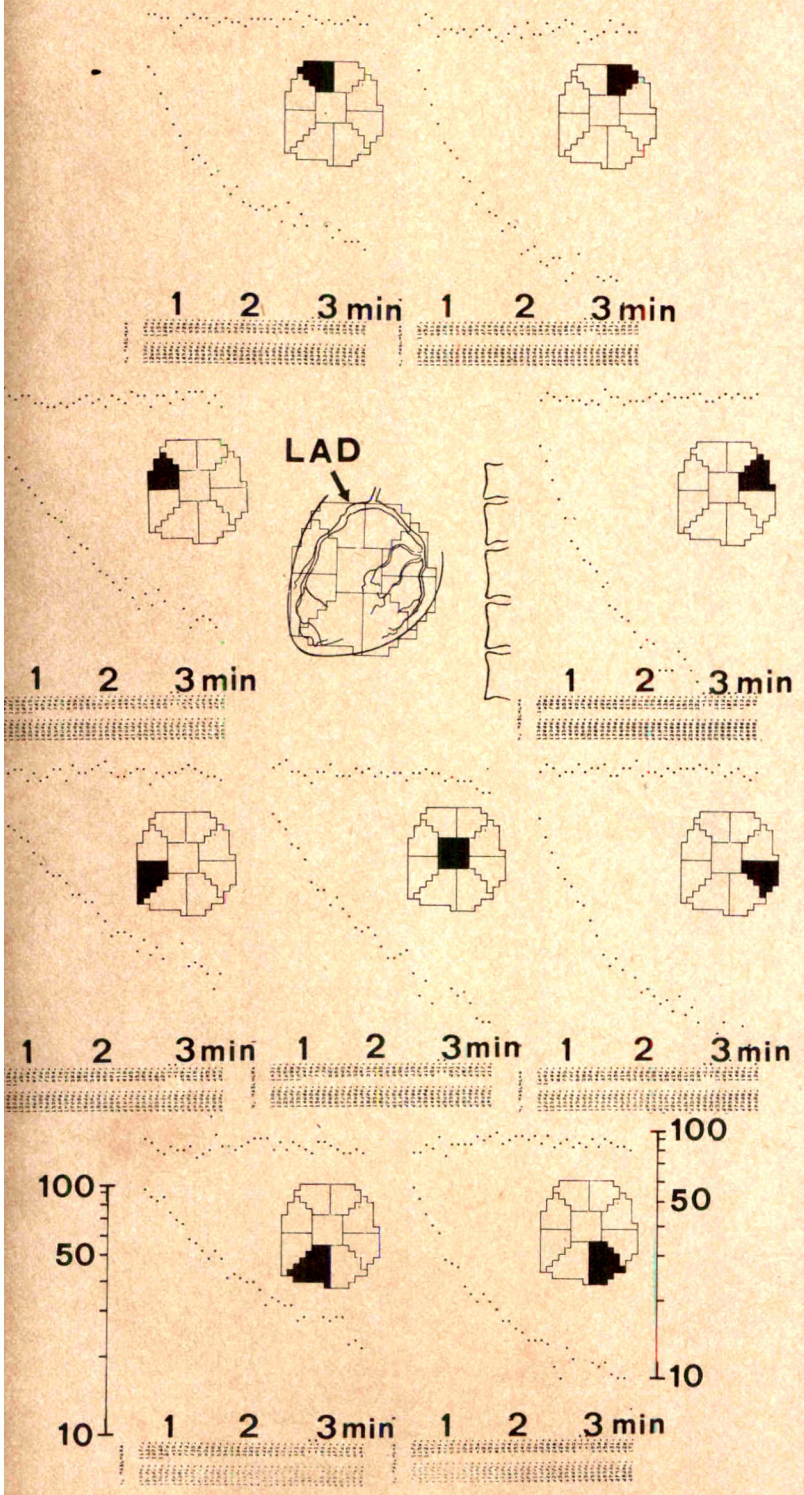


FIGURE 4. Alterations of regional washout slopes induced by pacing above the anginal threshold immediately after the injection of xenon in a patient with critical stenosis of the left anterior descending coronary artery (LAD) as the unique lesion. Counting geometry remains constant. The rate of washout becomes much slower than during rest in the areas distal to the obstructed vessel.

tional reduction of myocardial perfusion may play an important role in the extension and duration of ischemia. An increase of left ventricular diastolic pressure, documented in some of our cases, could account in part for this functional reduction of perfusion,[52] but secondary vasoconstrictor mechanisms, such as those involved in the genesis of "spontaneous" angina,[53] cannot be ruled out.

Pathogenesis of variant angina: Because of their noninvasive nature, the radioactive potassium and similar methods[28,54–56] are suitable for studies of the seriously ill patients admitted to the coronary care unit. After a series of measurements of myocardial clearance of rubidium-86 made with use of a precordial counter[22] on admission and during recovery in a group of patients with acute myocardial infarction and after several methodologic studies,[57–59] we concluded that only imaging devices could provide the desired information. They allow the identification of cardiac borders and hence the inclusion of the whole heart in the counting field, and provide images of the myocardial distribution of the indicator. However, quantification of myocardial blood flow requires that two additional conditions be met: (1) Myocardial tracer uptake must be measured while the amount of indicator not extracted during the first myocardial circulation is balanced by the amount that reenters the coronary arteries with recirculation; and (2) the contribution of intravascular and pericardial activity must be subtracted from the counting rate obtained over the cardiac area. The available data indicate that the first condition is fulfilled only during the first 1 to 2 minutes after injection. At this time intravascular activity is significant and therefore must be subtracted according to the method previously proposed.[28,59]

A series of studies on the pathogenic mechanisms of variant angina, based on continuous right and left ventricular pressure monitoring, failed to reveal a hemodynamic change that could increase myocardial metabolic demands before the attacks of spontaneous angina.[53] Therefore we decided to study regional myocardial perfusion in these patients during the spontaneous anginal attacks. The purpose of our study was to investigate whether an acute reduction of myocardial blood supply was responsible for the angina in these patients. This possibility was suggested by the angiographic observations during an attack of complete occlusion by coronary arterial spasms of the vessel that

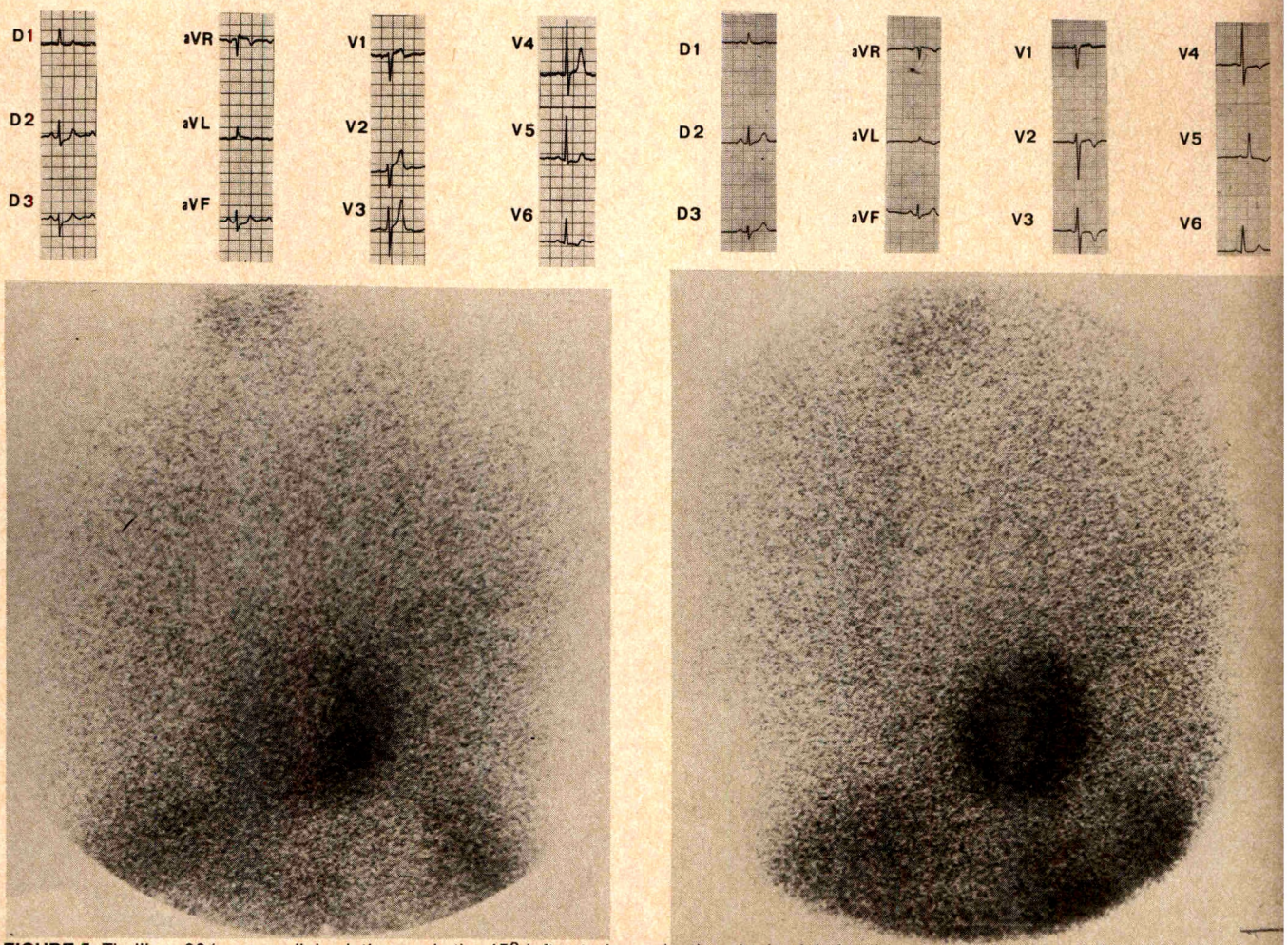


FIGURE 5. Thallium-201 myocardial scintigrams in the 45° left anterior projection obtained during "spontaneous" angina **(left)** and under control conditions without angina **(right).** During angina the electrocardiogram showed marked S-T segment elevation in leads V_1 to V_4. A severe transmural deficit of perfusion was observed in the anterior wall and septum during angina.

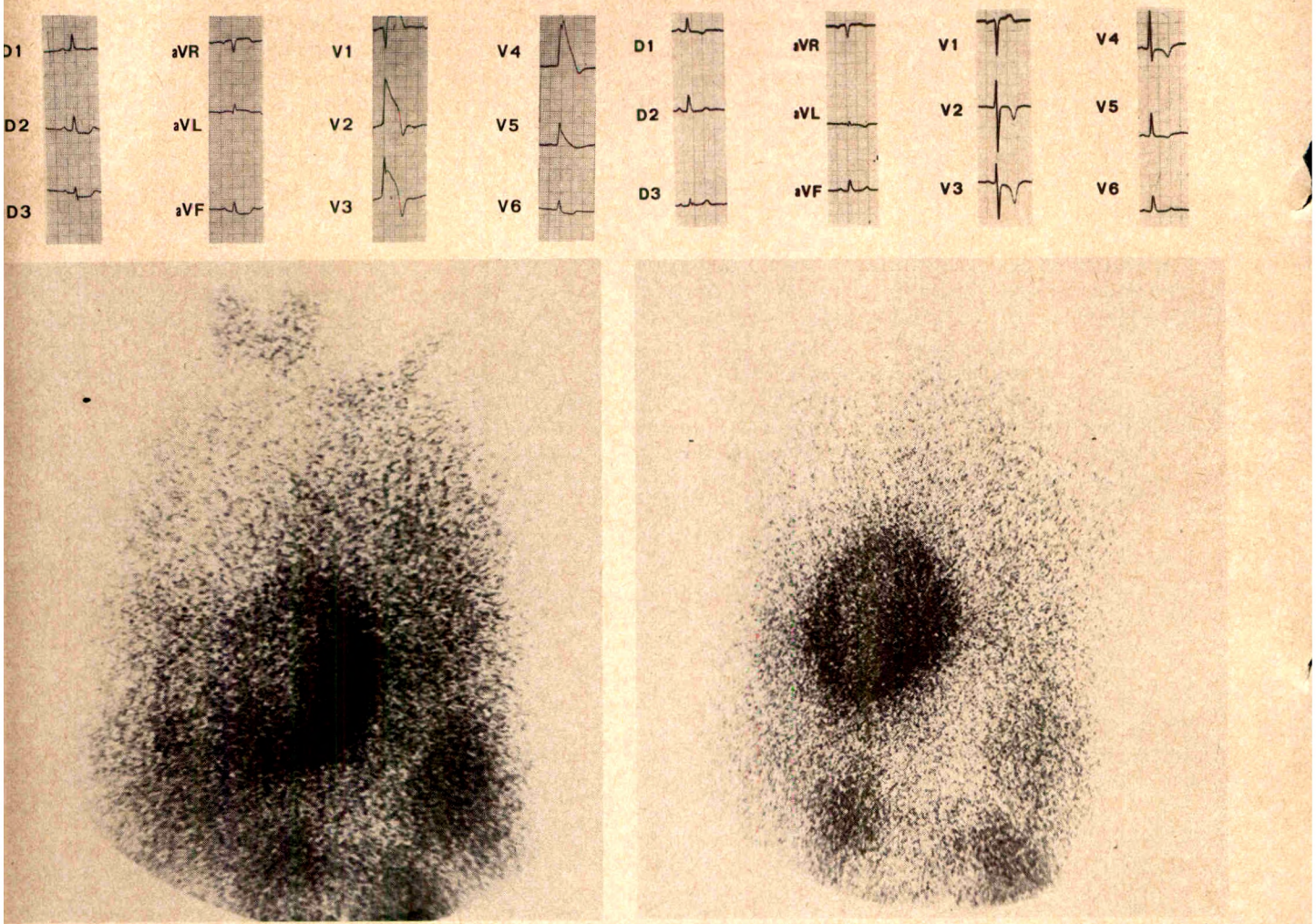


FIGURE 6. Thallium-201 scintigram in a patient during S-T segment elevation in leads V_1 to V_5 **(left)** and under control conditions without angina **(right).** In this patient a severe deficit of perfusion in the anterior left ventricular wall and septum was observed during angina.

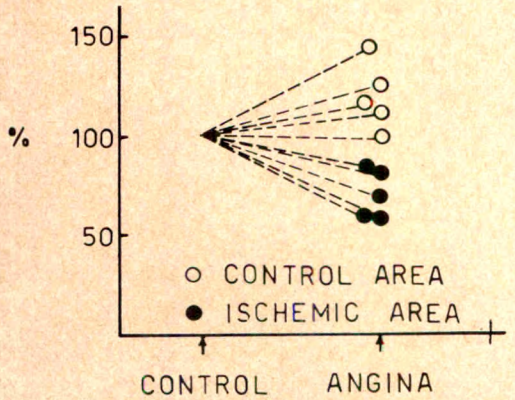


FIGURE 7. Percent changes in densitometric readings in the ischemic and control areas of myocardium. Readings in both areas in the scintigram obtained in the absence of symptoms are expressed as 100 percent. In all five cases (four with anterior, one with diaphragmatic ischemia), for the same injected dose an obvious reduction in accumulation of thallium-201 (TL) occurs in the ischemic zones, whereas uptake remains constant or increases in the control areas. The actual flow reduction in some areas of the ischemic myocardium must be much larger than indicated by this measurement.

perfused the myocardial territory corresponding to the site of S-T segment elevation.[53]

The attacks, although quite frequent (10 to 30/day), could not be predicted, and therefore our observations were limited to the semiquantitative methods. We injected equal amounts of thallium-201 (1 mCi) during a spontaneous attack and about a week later in the absence of symptoms. Life-size scintigrams were obtained using a jumbo Toshiba gamma camera and a high resolution collimator in the left anterior oblique, left lateral and anteroposterior projections between 5 and 15 minutes after the injection. The same procedure and technique were used in the two measurements. The analysis of the myocardial scintigrams was performed by visual inspection and by densitometric measurements on the film. During the anginal attack the injection was performed at the time of the appearance of the S-T segment elevation and the patient was immediately moved (in his bed) to the gamma camera room during electrocardiographic monitoring. In the patients studied to date, the attack lasted 3 to 5 minutes and was not

preceded by changes in heart rate or blood pressure. All myocardial scintigrams obtained during the attack showed a large transmural zone of reduced thallium-201 uptake (Fig. 5 and 6). Comparison of regional myocardial activity in the scintigrams performed at rest and during the attack with that in surrounding regions revealed that the reduction of perfusion to the ischemic areas was not related to increased uptake in the healthy areas. Thus an absolute reduction of tracer uptake in the ischemic areas and not a large increase of uptake in the normal myocardium was responsible for the relative differences of perfusion observed in the scintigram.[60]

Densitometric measurements allowed the quantification of regional thallium uptake (Fig. 7). These densitometric measurements underestimated the extent of ischemia because in the two-dimensional scintigram the counts in one area result from all the activity included within the solid angle outlined by its borders; it is unlikely that ischemia may involve to the same extent the myocardium included in the solid angle corresponding to the area showing the most obvious deficit of perfusion. The extent of ischemia is also underestimated on the basis of two theoretical considerations: (1) The clearance of the potassium tracer is greater at low than at high levels of flow[61]; (2) the ischemic tissues (if ischemia does not persist up to the time of the measurement) have a greater net extraction of the tracer than the normally perfused muscle during restoration of normal flow, because of the greater blood-tissue gradient (having received less tracer during the period of ischemia).

Although semiquantitative, these regional myocardial blood flow studies confirm the hypothesis that variant angina is caused by an acute severe transmural reduction of myocardial blood supply as a result of coronary vasoconstriction.[53,60]

Conclusions

The interdisciplinary application of nuclear medicine and cardiovascular techniques in the cardiac catheterization laboratory and the coronary care unit has contributed substantially to the fields of cardiopulmonary physiology and pathophysiology. The use of indicator-dilution principles with external counting has provided insight into the hemodynamic control of pulmonary blood volume under conditions in which combined right and left cardiac catheterization techniques were not applicable. The combined application of coronary catheterization and regional radioisotopic imaging has shown the presence of localized myocardial ischemia in patients with critical coronary stenosis at rest and the occurrence of localized functional impairment of myocardial perfusion during angina induced by pacing. Finally, during continuous monitoring in the coronary care unit, myocardial imaging has shown that so-called variant angina was associated with a massive transmural reduction of regional myocardial perfusion.

We hope that these observations provide a stimulus for further applications of nuclear medicine techniques in cardiology.

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Organization of Cardiovascular Nuclear Medicine Units

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Progress in the development of cardiovascular nuclear medicine can be accelerated by close cooperation between cardiologists and nuclear medicine physicians in the planning, performance and interpretation of diagnostic tracer studies. The special needs of patients with acûte cardiovascular disorders often require supplementation of the hospital's central nuclear medical facility with one or more satellite units in or near the coronary care unit, cardiac operating suite, postoperative intensive care unit or emergency room. Newly emerging noninvasive cardiac diagnostic laboratories should be equipped to perform certain nuclear medicine procedures. Selected nuclear diagnostic procedures also can provide useful supplemental information during cardiac catheterization and angiography.

Although radioactive tracer techniques were among the earliest noninvasive procedures for obtaining quantitative information about the cardiovascular system, only recent technical developments in nuclear instrumentation and radioindicators have brought such studies of the heart and circulation into more general clinical use. Many applications, while extremely promising, are still investigational and occupy an intermediate stage between early clinical testing and broad routine use. During this developmental period, in which procedures are constantly evaluated for their clinical utility, questions arise as to the relative usefulness of the various tests, the priorities for their availability, and the optimal organization of hospital and clinical services for the greatest benefit of patients and most efficient utilization of resources.

I shall try to answer six questions concerning these matters, recognizing that the rate of technologic advances and translation to practice is so rapid that my conclusions may be similarly subject to change. My goal is to provide a matrix for discussion and decision making that can accommodate new developments.

Which Cardiovascular Nuclear Medicine Procedures Should Be Available?

The answer to this question depends to a great extent on the patients to be served (for example, those with congenital heart disease, acquired heart disease or peripheral vascular disease) and the diagnostic and therapeutic procedures to be offered (such as cardiac catheterization, coronary arteriography, coronary bypass grafting, acute coronary care, reconstructive cardiovascular surgery) (Table I).

In hospitals and clinics where many patients with congenital heart disease are studied, radionuclide angiography for detecting, localizing and quantifying intracardiac shunts has proved useful. In institutions where reconstructive cardiovascular surgery for congenital heart disease is performed, it is important to have available facilities for radionuclide arteriography and venography, regional pulmonary perfusion and ventilation studies and brain scanning for detecting and localizing cerebral

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emboli and abscesses. In evaluating patients with acquired cardiac valve disease, one should have available radionuclide angiographic and regional pulmonary perfusion studies as measures of pulmonary venous hypertension.

In assessing the presence and severity of coronary artery disease, noninvasive methods for determining regional myocardial perfusion at rest and after exercise can be helpful. Because regional contractility is a major factor in the outcome of coronary bypass surgery, studies of ventricular wall motion and performance are important in planning such surgery. When coronary angiography is performed, measurement of regional perfusion as part of the cardiac catheterization procedure can give significant physiologic information to supplement the structural information about the coronary arteries.

In acute coronary care units and intensive postoperative cardiovascular care units of hospitals, the usefulness of certain procedures has either been demonstrated or shown considerable promise. These procedures include: acute myocardial infarct visualization, radiocardiography for assessing cardiac output and pulmonary vascular volume with use of pulmonary transit time measurements, radionuclide angiography, measurements of ventricular wall motion and performance, assessment of regional pulmonary perfusion and ventilation and measurement of certain compartmental volumes including red cell volume, plasma volume and, to a lesser extent, exchangeable sodium and total body water.

Where peripheral vascular disease is common, radionuclide arteriography and venography and regional pulmonary perfusion and ventilation studies for associated thromboembolic disease should be provided.

Where significant numbers of patients are being treated for congestive heart failure with digitalis drugs, assays for these pharmaceutical agents should also be available.

Where in the Hospital Should Cardiovascular Nuclear Medicine Procedures Be Available?

In small hospitals several procedures should be available routinely in the central nuclear medicine facility. As a minimum, small institutions should be prepared to perform radionuclide angiography, regional myocardial perfusion measurements using potassium analogs such as thallium-201, radionuclide arteriography and venography, acute infarct imaging, regional pulmonary perfusion and ventilation studies, digoxin and digitoxin assays, erythrocyte and plasma volume measurements and cerebral circulation studies as well as renal function measurements.

The scope of nuclear medicine examinations is so great that hospitals caring for many patients with cardiovascular disease may elect to have these procedures available in more than one location. In hospitals with acute coronary care or intensive care units, the capability for noninvasive physiologic measurements using radionuclide techniques can contribute substantially to the care of patients with cardiovascular disease. If a scintillation camera cannot be devoted exclusively to

TABLE I

Principal Cardiovascular Nuclear Medicine Procedures Grouped According to Their Utility in Various Conditions

Cardiovascular Nuclear Medicine Examinations	Congenital Heart Disease	Cardiac Valve Disease	Coronary Artery Disease	Acute Coronary Care and Intensive Postoperative Care	Peripheral Vascular Disease	Hypertension
Radiocardiography (determination of cardiac output, transpulmonary transit times, ejection fraction)				+		
Radionuclide angiography						
a. Qualitative: chamber delineation	+	+		+		
b. Quantitative: shunt detection-localization-quantification, stroke volume, ejection fraction, regurgitant fraction	+	+	+	+		
Ventricular wall motion and performance measurements			+	+		
				+		
Acute infarct visualization						
Regional myocardial perfusion studies						
a. Noninvasive (e.g., T1-201)			+	+		
b. Invasive (e.g., microspheres, Xe-133)			+			
Radionuclide arteriography and venography	+				+	+
Regional pulmonary perfusion and ventilation	+	+		+	+	
Drug and hormonal assays						
a. Digoxin and digitoxin	+	+	+	+		+
b. Angiotensin I						
Red blood cell and plasma volumes				+		+
Brain scanning	+					+
Relative renal function measurements						+

these patients or if a mobile instrument cannot be brought from the central nuclear medicine facility, a small simply collimated radiation detector or probe can be used. Even without more sophisticated data processing, such devices may be used for measurement of cardiac output and transpulmonary transit time so that pulmonary vascular volume can be estimated. When computer facilities are available and can be interfaced either by direct access through long distance telephone lines or by dedicated data acquisition devices, more detailed information can be obtained. With a scintillation camera in the coronary care unit one can demonstrate acute myocardial infarcts using technetium-labeled phosphate compounds or reveal underperfused regions of the myocardium using cationic substances such as thallium-201. Qualitative radionuclide angiography can be performed to detect acute changes in ventricular volumes. Interfacing of the gamma camera to a computer allows quantitative measurements of ventricular wall motion, stroke volume, ejection fraction and regurgitant fraction.

In postoperative intensive care units nuclear instrumentation is useful in treating patients who have had reparative or reconstructive surgery for congenital heart disease, particularly left to right shunts; pulmonary dilution curves obtained sequentially after surgery can be used to determine whether shunt closure has been maintained; when there has been translocation of major blood vessels to augment or restore pulmonary blood flow, patency of such vessels can be ascertained. Such assessment can often be made with use of a simple nonimaging detector alone. A scintillation camera provides the opportunity for measuring regional ventilation and perfusion of the lungs as well as ventricular wall motion and ejection fraction. The procedures useful in the coronary care unit are also helpful in the postoperative care of patients who have had coronary bypass surgery. In addition to the ability to measure ventricular wall motion and myocardial perfusion, the ability to measure regional ventilation and perfusion of the lungs is useful in patients in whom prolonged postoperative bed rest increases the threat of pulmonary embolism, atelectasis or pneumonia.

Nuclear medicine procedures can be used in the cardiac operating room to evaluate the results of surgery before the chest is closed. This is particularly useful in complex reconstructive operations for congenital heart disease; for example, the patency of intracardiac communications and vascular channels can be determined. The pulmonary dilution curve can also be used to determine whether a shunt has remained closed. Special devices can be used to assess the functioning of coronary bypass grafts at the time the anastomosis is completed.

In busy cardiac clinics or noninvasive cardiac facilities, nuclear medicine procedures can be used to obtain important diagnostic information. For example, the quantitative radionuclide angiocardiogram is a simple method for following the status of left to right shunts, particularly in patients with a ventricular septal defect. In clinics where many patients with acquired heart disease are seen, nuclear procedures make it possible to evaluate ventricular wall motion and function, pulmonary vascular volume and regional myocardial perfusion. When symptomatic patients are being screened for coronary artery disease, myocardial perfusion before and after exercise can be evaluated in conjunction with electrocardiographic studies.

Nuclear procedures can also add information to the data obtained at cardiac catheterization and angiography. Labeled radioactive microspheres can be injected to delineate the relative perfusion to various parts of the myocardium during rest and after induced hyperemia. Alternatively, radioxenon or related radioactive gases, such as krypton-81m, can be injected to obtain an estimate of regional blood flow in relation to morphologic evidence of disease as seen in the angiographic and ventriculographic studies. The combination of coronary arteriography, ventriculography and nuclear studies gives a more comprehensive picture of the state of coronary circulation and its related physiology than nonnuclear studies alone.

In busy emergency rooms where the movement of patients can be time-consuming and hazardous, it is often useful to have nuclear capabilities available. In addition to the detection of pulmonary embolism, nu-

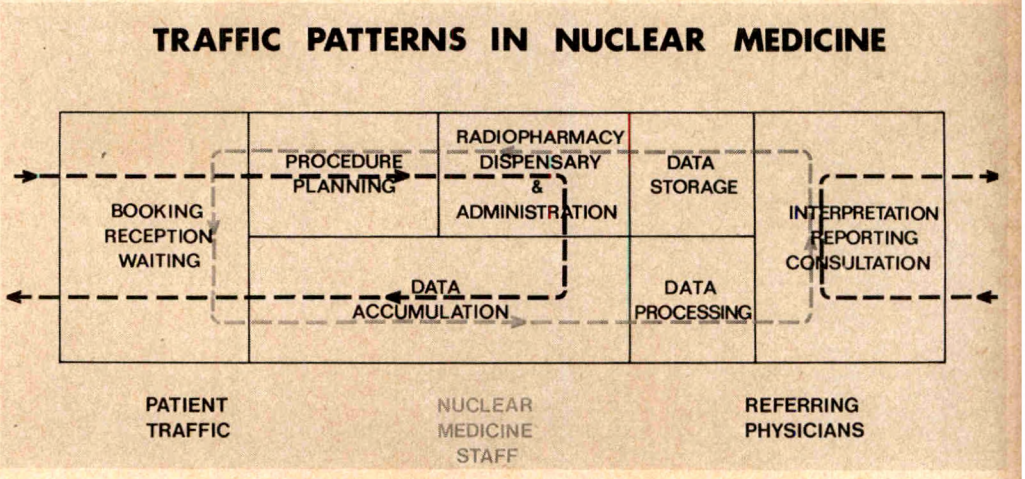


FIGURE 1. Functional relations among the elements of the diagnostic nuclear medicine process.

clear procedures can help detect acute coronary thrombosis with myocardial infarction, evaluate acute cardiac emergencies such as papillary muscle rupture and, in infants, help in the differential diagnosis of cardiac and pulmonary sources of cyanosis.

A major characteristic of nuclear medicine procedures is that they are noninvasive and thus can be used early and often in the diagnostic process. Although the majority of patients seen in a central nuclear medicine facility today come from the inpatient medical service, it is likely that in the future increasing numbers of patients will come from ambulatory outpatient services. Therefore, the central facility should be easily accessible to outpatients. Radiation shielding and structural requirements are minimal and should not be considered obstacles to locating the facility close to patient areas.

How Should Cardiovascular Nuclear Medicine Facilities Be Designed?

The performance of nuclear medicine procedures in the coronary care unit, intensive care unit, cardiac operating room, catheterization-angiographic laboratory or emergency room requires the immediate availability of specialized equipment and committed storage space for instruments and radiopharmaceutical agents. When these facilities are at some distance from the central nuclear medicine unit, the equipment must be used frequently enough to maintain adequate quality in the performance of the tests.

In the central nuclear medicine facility as well as in satellite nuclear medicine units, the functional relations at various stages of procedure preparation, examination and communication are demonstrated in Figure 1. The details of spatial requirements are given elsewhere.[1]

What Equipment and Supplies Are Necessary?

The most generally useful piece of equipment for cardiovascular nuclear medical studies is the scintillation camera. Because of the spatial and temporal resolution required for cardiovascular work, especially of regional myocardial blood flow and radionuclide angiocardiography, the newest generation of scintillation camera systems is recommended. These systems should have a spatial resolution of 6 mm or better in the range of 120 to 200 keV, measured as the full width at half maximum of line spread functions with a radioactive source at the face of the collimator. Count rates of up to 100,000 counts/sec should be obtained without excessive dead-time losses.

The availability of a digital computer greatly enhances the utility of many cardiovascular studies. The computer facilitates the obtaining of certain quantitative measurements such as stroke volume and ventricular ejection fraction and improves image quality, thereby facilitating demonstration of regional abnormalities in ventricular wall motion. A "hard wire" special purpose system or a general purpose programmable computer can be used.

Nonimaging detectors, sometimes called "probes," can be used instead of scintillation cameras to measure cardiac output, ejection fraction, left to right shunting, transpulmonary transit time and arteriovenous shunting in the peripheral circulation. When such a device is used for radiocardiography, it must be equipped with special collimators and provide for a rapid temporal response. Dose calibrators are necessary to assess the activity of the radiopharmaceutical agents used for in vivo procedures. The performance of in vitro tests (such as drug and hormone assays) and measurement of compartmental erythrocyte and plasma volumes requires a scintillation well counter.

Cardiovascular nuclear medicine studies require that a number of short-lived radiopharmaceutical agents be available on a continuing or contingency basis. These include technetium-99m as pertechnetate, technetium albumin or technetium red blood cells. If technetium albumin is used for quantitative studies of ejection fraction, it is important that no significant quantities of unbound technetium be present. Because of difficulties in obtaining suitable technetium albumin preparations, some clinics have been using technetium red blood cells labeled in vivo as an intravascular indicator.

Acute myocardial infarcts can be delineated with various technetium-labeled chelates, but at the present moment the phosphorus compounds such as pyrophosphates and diphosphonates seem to give the best results. For noninvasive assessment of regional myocardial perfusion, the monovalent cations thallium-201 or rubidium-81 are preferable. For regional myocardial and pulmonary blood flow as well as regional pulmonary ventilation studies, xenon-133 is most commonly available although xenon-127 has important physical advantages, and krypton-81m may soon be available. The advantage of the latter is its 13 second half-life. Technetium and iodine-131 or indium-113m labeled particles are used for myocardial perfusion studies during coronary arteriography and for peripheral arteriographic examinations.

The computer programs for certain cardiovascular nuclear medicine examinations are now well established and some of these are currently available in "hard-wired" systems. The manufacturers of these systems

TABLE II

Personnel Requirements for Cardiovascular Nuclear Medicine Services

Staff	Duties
Clinical	
Escort messengers	Transportation of patients
Receptionists	Scheduling, reception
Technologists	Procedure planning, radiopharmaceutical administration, data accumulation, data processing
Physicians	Procedure planning, radiopharmaceutical administration, interpretation, reporting, consultation
Support	
Nuclear medicine chemists	Radiopharmaceutical development and preparation
Nuclear medicine physicists	Acquisition and maintenance
Clerks	Report preparation

will attempt to provide the newer computer codes as they become available. For the present, laboratories with general computer facilities may make use of newer codes documented and distributed by the Computer Committee of The Society of Nuclear Medicine.

What Personnel Are Required to Perform These Studies?

Because nuclear medicine procedures require knowledge of advanced nuclear and computer technology, physiology and pathophysiology, and clinical judgment, personnel with diverse expertise are needed (Table II). In general, personnel can be divided into two groups, those who deal directly with patients (the clinical staff) and those who deal only indirectly with patients (the support staff).[2] There is of course some overlap in their activities.

Nuclear medicine physicians and cardiologists evaluate patients before every diagnostic study, supervise the technical aspects of the study (for example, advising technologists on the adequacy of the data obtained), interpret examination results and consult with referring physicians. If a physician's duties are restricted to these activities, he should be able to care for 12 to 20 patients a day.

Technologists must understand the basic principles of radiation physics and radiopharmaceutical chemistry as well as the fundamentals of nuclear instrumentation. They should be experts in the operation of nuclear instruments and be able to perform calibration checks, quality control procedures and minor maintenance duties. They should understand the problems of caring for sick people and their families, be skilled in patient positioning and know sufficient anatomy and physiology to understand the morphophysiologic basis of nuclear procedures and the consequences of patient and position variation. They should know sufficient radiation hygiene to minimize staff and patient radiation exposure and to perform simple decontamination procedures. Because certain cardiovascular procedures are performed on an emergency basis and cannot be repeated without some degradation of information, it is essential that technologists who perform these procedures have adequate experience. On the average, one technologist can assume responsibility for 8 to 10 major in vivo procedures a day.

In many clinics an experienced technologist prepares the radiopharmaceutical agents but in major medical centers this task is generally performed by a radiopharmaceutical chemist or radiopharmacist. This is particularly true when special radioindicators need to be prepared.

The services of a nuclear medicine physicist should be available on a full or part time basis. His responsibilities include radiation safety, quality control of instrumentation, teaching of medical physics and nuclear instrumentation and translation of new technology to practice. Skills in computer programming are also desirable. The maintenance of nuclear medicine equipment, whether performed in-house or under service contract, should be under his jurisdiction.

How Should Cardiovascular Nuclear Medicine Be Administered?

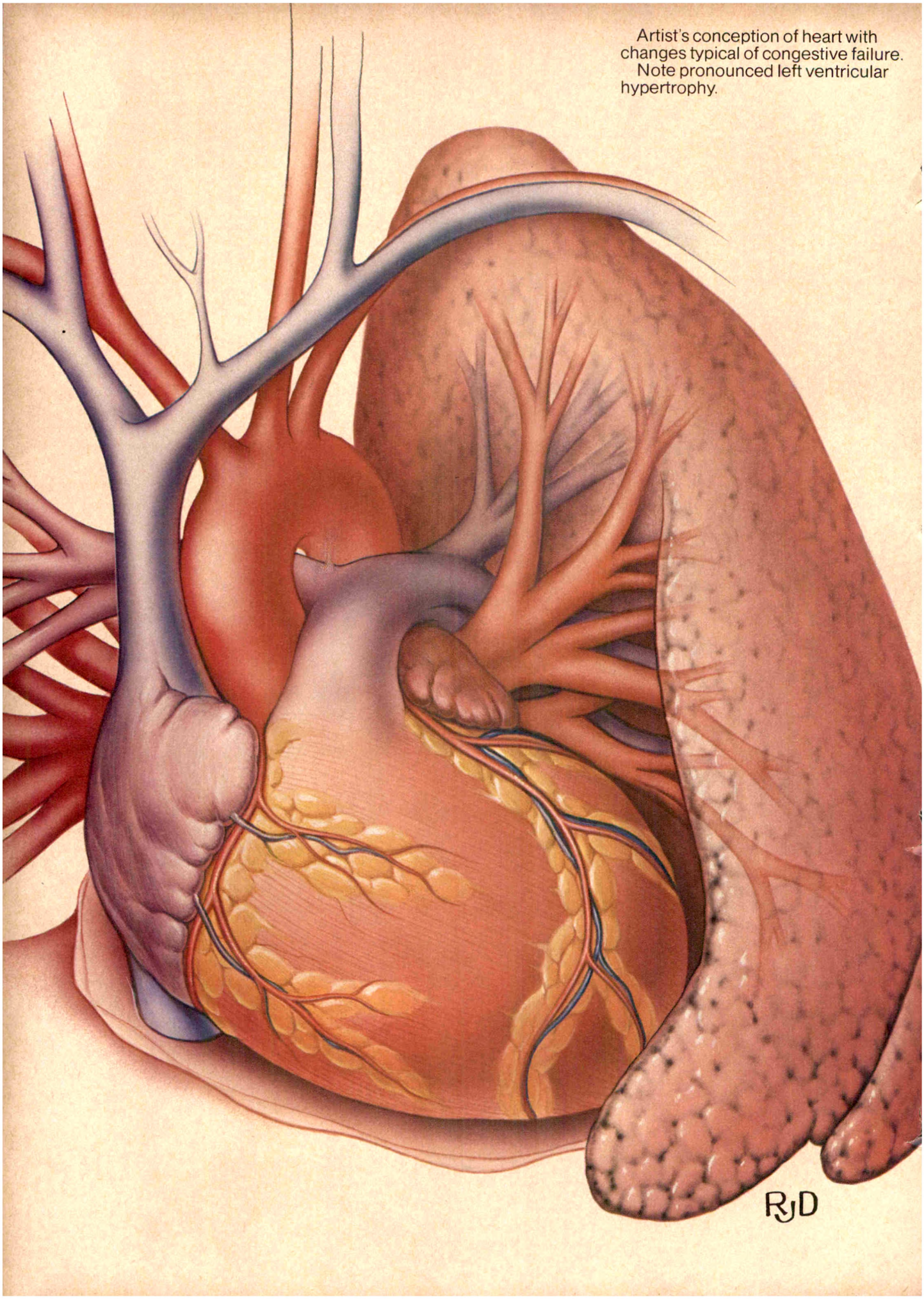
The planning, performance and interpretation of cardiovascular nuclear medicine studies require, in addition to sound clinical judgment, a broad and intensive knowledge of nuclear medicine instrumentation, radiopharmaceutical agents and cardiovascular physiology. Radionuclide cardiovascular procedures demand the utmost in nuclear medical sophistication: an in-depth knowledge of the capabilities and limitations of instruments, detailed understanding of tracer kinetics and the vagaries of radioindicators and familiarity with data processing, usually by digital computer, of physiologic and morphologic data. Clinically, the demands are equally as great because many of the patients studied are extremely ill, have complicated pathophysiologic problems, and require the most exacting cardiologic judgment-making, including decisions about the performance and timing of cardiac surgery. It is possible that these intellectual and technical requirements can be met by a single person such as a cardiologist with special training in nuclear medicine or a specialist in nuclear medicine who has spent an equal time in the study of cardiovascular disease. Today, however, these skills more probably will require the active collaboration of two or more specialists.

Therefore, performance of cardiovascular nuclear studies should be a joint responsibility, shared by specialists in nuclear medicine and cardiologists who accept the obligation to keep abreast of advances in this rapidly changing field, particularly with regard to instrumentation and methodology. The technical aspects of examinations, from the preparation of radiopharmaceutical agents to the selection of instrumentation and the supervision of technologists, are clearly in the domain of the nuclear medicine specialist. With his training, he should also be responsible for the safety, technical performance and quality control of the unit. The selection of procedures to be performed, the location of cardiovascular nuclear medicine facilities and the planning of examinations for individual patients must be a cooperative effort between cardiologists and their nuclear medicine colleagues. If either cardiologists or nuclear medicine specialists attempt to operate this satellite service independently, it will probably fail or perform ineffectively.

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Artist's conception of heart with changes typical of congestive failure. Note pronounced left ventricular hypertrophy.

In congestive heart failure...

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Warnings—Potassium supplementation may cause hyperkalemia and is not indicated unless a glucocorticoid is also given. Discontinue potassium supplementation if hyperkalemia develops. **Usage of any drug in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the mother and fetus.**

In a 78-week chronic toxicity study, rats were given daily oral doses of spironolactone approximately 30, 90 and 300 times the usual daily human therapeutic dose (100 mg. per day). The results of this study demonstrated a dose-related, statistically significant increase in the occurrence of benign adenomas of the testes and thyroid gland. Similar findings have not been demonstrated in other animal studies. In view of the marked differences in spironolactone metabolism by the rat and by man, the relationship of this finding to the possible development of tumors in humans is unknown.

Precautions—Patients should be checked carefully since electrolyte imbalance may occur. Although usually insignificant, hyperkalemia may be serious when renal impairment exists; deaths have occurred. Hyponatremia, manifested by dryness of the mouth, thirst, lethargy and drowsiness, together with a low serum sodium may be caused or aggravated, especially when Aldactone is combined with other diuretics. Elevation of BUN may occur, especially with preexisting renal impairment. Mild acidosis may occur. Reduce the dosage of other antihypertensive drugs, particularly the ganglionic blocking agents, by at least 50 percent when adding Aldactone since it potentiates their action. The physician should be alert to the possible onset of gynecomastia.

Adverse Reactions—Drowsiness, lethargy, headache, diarrhea and other gastrointestinal symptoms, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, gynecomastia, inability to achieve or maintain erection, androgenic effects, including hirsutism, irregular menses and deepening voice. Adverse reactions are usually reversible. In rare instances gynecomastia may persist.

Dosage and Administration—**For essential hypertension in adults** the initial daily dosage is 50 to 100 mg. in divided doses. Aldactone may be combined with a thiazide diuretic if necessary. Continue treatment for two weeks or longer since the maximal response may not occur sooner. Adjust subsequent dosage according to response of patient.

For edema in adults initial daily dosage is 100 mg. in divided doses. Continue medication for at least five days to determine diuretic response; add a thiazide or organic mercurial if adequate diuretic response has not occurred. Aldactone dosage should not be changed when other therapy is added. A daily dosage of Aldactone considerably greater than 75 mg. may be given if necessary.

A glucocorticoid, such as 15 to 20 mg. of prednisone daily, may be desirable for patients with extremely resistant edema which does not respond adequately to Aldactone and a conventional diuretic. Observe the usual precautions applicable to glucocorticoid therapy; supplemental potassium will often be necessary. Such patients frequently have an associated hyponatremia—restriction of fluid intake to 1 liter per day or administration of mannitol or urea may be required (these measures are contraindicated in patients with uremia or severely impaired renal function). Mannitol is contraindicated in patients with congestive heart failure, and urea is contraindicated with a history or signs of hepatic coma unless the patient is receiving antibiotics orally to "sterilize" the gastrointestinal tract.

Glucocorticoids should usually be given first to patients with nephrosis since Aldactone, although useful for diuresis, will not directly affect the basic pathologic process.

For children the daily dosage should provide 1.5 mg. of Aldactone per pound of body weight.

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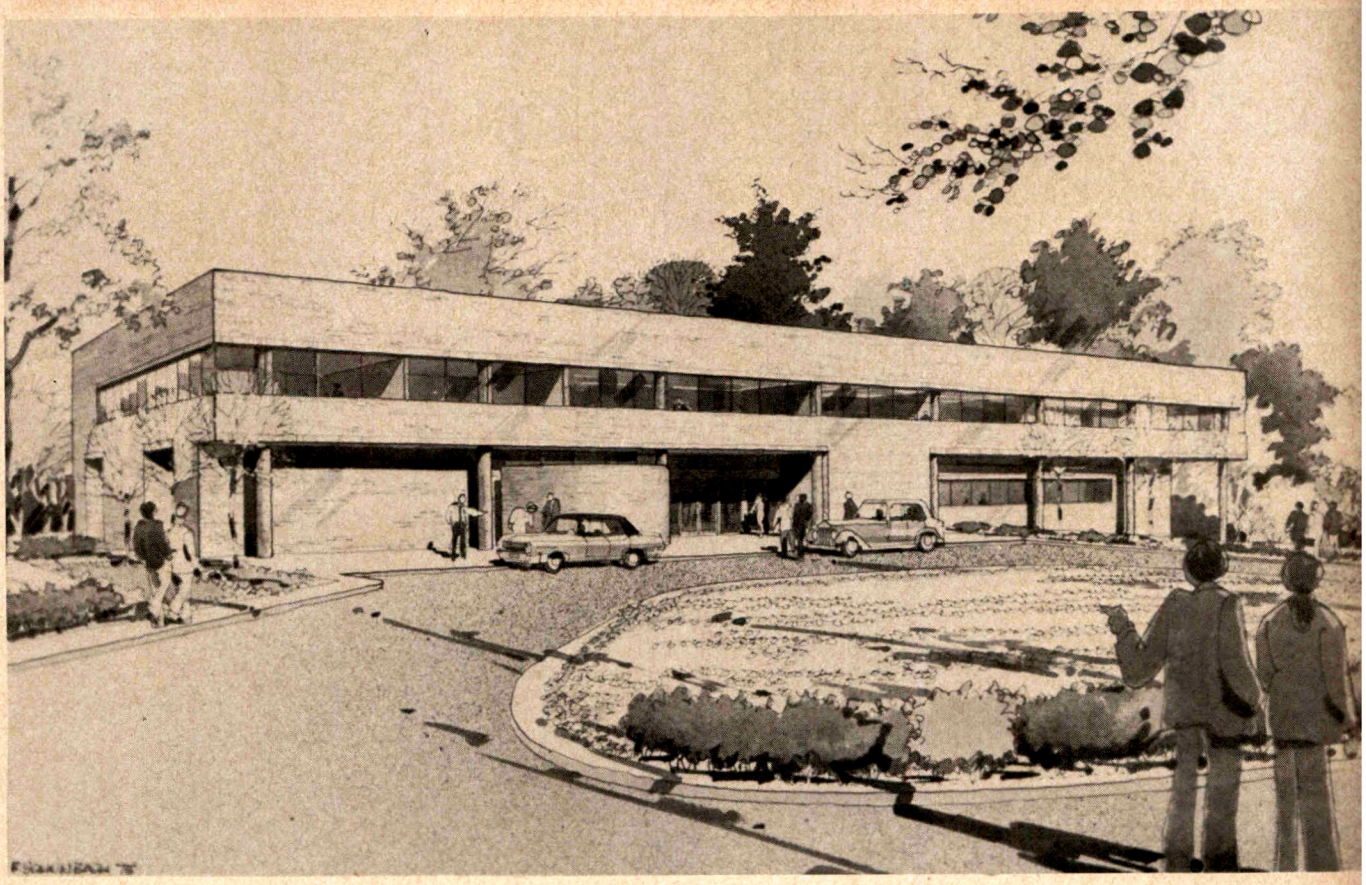
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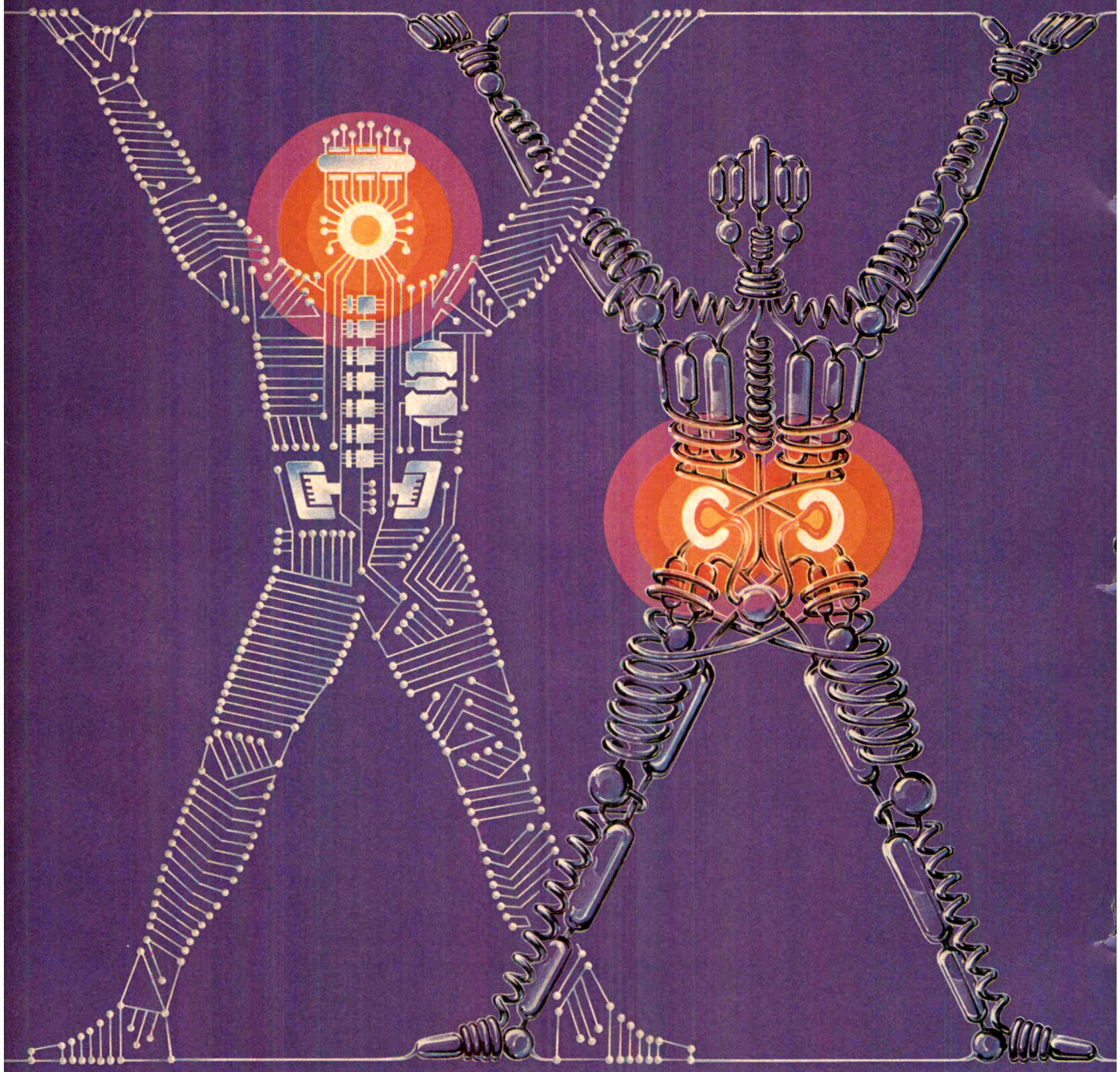
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Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

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SYMPOSIUM ON HYPERTENSION: PART III

Sodium and Potassium, Catecholamines, Renin and Adrenal Steroids As Causal Factors. Hypertension and Atherosclerosis. Clonidine Treatment and the Renin Axis

JOHN H. LARAGH, MD, *Guest Editor*

Introduction

JOHN H. LARAGH, MD

New York, New York

In this issue we present the third section of a Symposium devoted to various aspects of the problem of high blood pressure, a problem that now appears as the greatest challenge yet afforded to physicians for preventive cardiology.

In part I of this Symposium,[1] new information was presented about the important role of beta adrenergic blocking drugs in the modern treatment of hypertension. When these drugs were first introduced some 10 years ago, they were used to treat cardiac arrhythmias and angina pectoris; animal research had provided no clue to their value in treating high blood pressure. In fact, in clinical studies these drugs had an undistinguished history as antihypertensive agents; many early reports described partial or questionable benefit. An important factor in their reevaluation in the United States was the relatively recent observation of their very powerful action in reducing renal renin secretion. It was thought that this action might largely explain the antihypertensive effectiveness of these drugs and, if renin levels were used as a baseline marker, might also tell the clinician which patients were likely to respond to this treatment.

In the second section of the Symposium[2] more information was provided on the burgeoning role of renin profiling in providing the clinician with baseline data for use in planning drug therapy. In addition, the timely subject of childhood hypertension and some new information about the physiology of renin secretion and of different chemical forms of renin was provided with a discussion of the clinical implications.

In this part III of the Symposium we present some timely reviews of findings and their clinical implications. First, Meneely and Battarbee review our state of knowledge with respect to the role of dietary electrolytes in the pathogenesis or induction of human and experimental hypertension. It is clear that salt appetite in "civilized" man is at least in part a phenomenon of custom. Probably the sodium intake is too high in most civilizations but critical experiments are necessary to determine whether massive efforts should be made to change it and, if so, what the optimal levels for sodium and potassium intake really are. Another important related question that needs solution relates to the issue of ideal dietary salt intake in patients receiving various types of antihypertensive therapy.

Hollander reviews another critical subject, the important role of hypertension in inducing or amplifying the progress of atherosclerotic disease, particularly that involving the heart and the brain. Although high blood pressure is known to be a major risk factor in cardiovascular disease, the exact nature of its effect remains to be defined. Hollander presents, quite objectively, the various factors now implicated and gives the reader suggestions for future approaches.

DeQuattro and his colleagues from Los Angeles present new information indicating that the large majority of patients with high renin forms of hypertension

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also have raised plasma catecholamine levels whereas those with low renin levels rarely exhibit this abnormality. This observation could be crucial to investigators interested in the possibly important link between sympathetic nervous system activity and renin secretion by the kidneys. The observation may also provide a further basis for understanding the unique effectiveness of sympathetic blocking drugs, beta blocking drugs in particular, in high renin forms of hypertension and relative lack of effectiveness in low renin states.

The next two papers deal with a problem now being intensively studied by several laboratories in the United States and abroad: the possible role of an as yet unidentified adrenocortical mineralocorticoid in causing some fraction of what is known as essential hypertension. First, Melby and Dale review their research and present their current position on this question. They are convinced that increased secretion of certain mineralocorticoids can initiate or perpetuate hypertension in man. In addition they view positively the possibility that 16-beta-hydroxy dehydroepiandrosterone (16 β-OH-DHEA) may also be a factor in animal and in human hypertension.

Ulick offers a contrasting view. On the basis of his own extensive steroid biochemical studies in relation to clinical medicine, he presents a rather convincing case against any possible role of 18-hydroxy DOC in human hypertension. Thus, although it is possible that an unidentified steroid may be a factor in human hypertension, I believe that at present, the clinician is forced to view with caution and circumspection any tentative claims of a causative relation. On the other hand, this area of research should be pursued with vigor until all possibilities have been thoroughly examined. Indeed, the ultimate role of known steroids such as aldosterone or even cortisol in the pathogenesis of human hypertension also remains to be fully explored and clarified.

In the final paper of the Symposium, Weber and his colleagues of our group analyze the mechanism of action of clonidine in the various subgroups of essential hypertension. Using renin profiling to classify these patients, they demonstrate that clonidine may have at least two mechanisms of antihypertensive action in man. The first seems to be related to suppression of renin secretion and produces impressive antihypertensive action in most patients with high and normal renin levels. A second and more delayed antihypertensive effect is manifest in all hypertensive patients after 4 or 5 days of treatment and is clearly due to mechanisms other than renin. This latter action accounts for the effectiveness of the drug in hypertensive patients with low renin levels. This longer-term antihypertensive action seems to be related to the inhibition of aldosterone production consequent to renin suppression, which minimizes long-term reactive volume retention during treatment. The study illustrates that with further use of renin and aldosterone profiling it will soon be possible to dissect out with more precision various components of the antihypertensive action of various drugs, which in turn should lead to simpler and more specific forms of therapy.

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High Sodium-Low Potassium Environment and Hypertension

GEORGE R. MENEELY, MD, FACC
HAROLD D. BATTARBEE, PhD

Shreveport, Louisiana

The high sodium-low potassium environment of civilized people, operating on a genetic substrate of susceptibility, is the cardinal factor in the genesis and perpetuation of "essential" hypertension. The noxious effects begin in childhood, when habits of excess salt consumption are acquired at the family table, and are perpetuated by continuing habit and by increasing use of convenience and snack foods with artificially high concentrations of sodium and low levels of potassium. Present methods of food preparation leach out the protective potassium. Extradietary sodium chloride is a condiment, not a requirement. Some primitive populations clearly preferred potassium chloride to sodium chloride.

Chronic expansion of extracellular fluid volume induced by excess salt consumption causes the central and peripheral circulatory regulatory mechanisms to work at cross purposes, resulting in increased arterial pressure. The protective effect of potassium is dramatic and easily demonstrable in animals and man but its mechanism is not known. It cannot be entirely a direct effect on blood pressure because rats protected with extra potassium against a moderately high salt intake live much longer than control rats but have the same elevated blood pressures. In hypertension with a demonstrable "cause," the high sodium-low potassium environment makes a bad matter worse.

In nature, feral man and his forebears were not confronted with excessive sodium and deficient potassium; indeed, the reverse was the case. Evolution has provided powerful mechanisms for conserving sodium and eliminating potassium, but no efficient physiologic mechanisms for conserving potassium and eliminating excess sodium. Most laboratory animal "control" diets contain an amount of sodium that fully suppresses aldosterone secretion, and the same is true of the "average" diet of the American people. Inadequate attention to dietary sodium and potassium makes many studies in both animals and man of uncertain validity.

Internally, essential hypertension is an exceedingly complex mosaic of physiologic interactions. Viewed from outside, it is a disorder for which genetic material sets the stage; excessive sodium precipitates it and perpetuates it. Extra salt makes all forms more rapidly progressive and accelerates the onset of terminal events; extra potassium is everywhere protective. When an entire population eats excessively of salt, hypertension will develop among those genetically susceptible, but epidemiologic studies of salt *versus* blood pressure will not show a relation of salt to hypertension. This is the *saturation effect.*

Low sodium diets are therapeutically effective but generally regarded as an impossible or an unnecessary nuisance. Effective prevention programs must be instituted at as early an age as possible. The efficacy of a prophylactic/therapeutic low sodium-high potassium diet should be weighed against the uncertain hazards of a lifetime of pill taking.

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This review is dedicated to the late Lewis K. Dahl: a warm friend, an esteemed colleague and a dedicated scientist.

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[There is another way to truth: by the minute examination of facts. That is the way of the scientist: a hard and a noble and a thankless way.

John Masefield, 1924.]

Elevated blood pressure is not a disease, it is a physiologic observation. Guyton and his co-workers[1] convey the idea succinctly: ". . . arterial pressure is the summed effect of the many different participating [physiologic] mechanisms." When elevation of the arterial pressure is persistent, we speak of hypertension. Physicians have long recognized that the sequence of events thereby set in train usually leads to impairments that are most significant ultimately in the eye, brain, heart or kidneys, alone or in combination. Sometimes a "cause" such as pyelonephritis can be found for the persistent elevation of blood pressure; more often it cannot. In this review we are concerned with the majority of hypertensive patients, those whose hypertension is essential and has no demonstrable cause.

Classification of Hypertensives

The etiologic classification of hypertensive subjects thus leaves the largest fraction unclassified, those whose disorder is, as described by Edgar Hull, idiopathic, cryptogenic and of unknown origin. Recent efforts at physiologic classification have more promise—for example, classification according to low, normal or high plasma renin activity.[2,3] In a recent editorial Krakoff[4] hopes that "expanded approaches to the pathogenesis of high blood pressure will eventually cause the term 'essential' to be dropped from our vocabulary . . . so that we can direct our attention to . . . [the] specific cardiovascular disorder and its appropriate management." However, there are forbidding obstacles. If one examines a schema of Guyton's systems analysis of the control of blood pressure, one sees that there are a rather large number of "participating mechanisms," any or all of which may go wrong and usually in several different ways.[1,5] The technical methods of control systems analysis are more familiar to engineers than to physicians but it is easy to predict, without much expertise in this matter, that the ultimate pathophysiologic classification will be complicated. In examining the fine structure of these systems, there is some danger that we may lose sight of some larger, simpler, perhaps more immediately urgent aspect of the problem. It is the purpose of this review to develop a thesis: that the high sodium-low potassium environment, operating on an appropriate genetic substrate, is a cardinal factor in "essential" hypertension and that, even among those whose hypertension is of known cause, a high sodium-low potassium environment usually makes a bad matter much worse.

The incidence of hypertension is large among adults whose parents were hypertensive. As Pickering[6] states, ". . . you tend to resemble your parents and the resemblance is quantitative . . . ." If both parents have hypertension, it will probably develop in two of three of their children; if only one parent has hypertension, it is likely to occur in one of three. Although hypertension represents a "disease of degree," [6,8] one can make statements about what the future is likely to hold for those whose pressures are in the upper ranges. Since the work of Janeway[9] in 1913, it has been known that death tends to occur sooner in persons with higher arterial pressures. At any level of elevated pressure, the younger the age, the greater is the reduction in life expectancy.[10] Sixteen percent of the American population aged 18 to 79 years has systolic blood pressure of 160 mm Hg or greater, or diastolic pressure of 95 mm Hg or greater, or both,[11] and the prevalence rate of hypertension ranges up to 40 percent in older age groups.[12,13] When diastolic pressure is 105 mm Hg or more, the risk of a first major coronary event is four times greater than when it is less than 85 mm Hg.[14] There are said to be 23 million Americans with high blood pressure. Life insurance underwriters have never had any illusions about the prognostic significance of hypertension.[15] Millions of children and youth can expect to have hypertension.[16]

It has become evident that children and young people who have blood pressures at the "upper limits of normal" are particularly prone to hypertension in adulthood. An appreciable fraction of this group may be hypertensive already, but the "upper limits of normal" at their age level is blurry. Generally, it is true for any young person that the higher the blood pressure, the more likely it is that frank hypertension will develop in middle or older middle age. This phenomenon, commonly called "tracking," is also seen in animal models.[17] Thus, there is a sort of sliding scale of decreasing probability of the development of significant hypertension as one moves from subjects with values in the highest deciles toward the larger majority of subjects with values in the middle quartiles. Nevertheless, among those with values in the higher ranges are some who will not become hypertensive, and in among those with values in the mid and lower ranges, many who will. Blood pressure measurement alone does not suffice to identify objectively and definitively those who stand in serious threat of future clinically significant hypertension. Criteria that address the underlying physiologic defect are needed to identify these young people. There are good reasons to believe that excessive dietary sodium and deficient dietary potassium play a cardinal role in the genesis of hypertension among the large fraction of our population which has a hereditary susceptibility to it. Further evidence indicates that the noxious effect begins in childhood where, as Dahl et al.[18,19] have pointed out, the habit of excess salt consumption is acquired at the family table. Meanwhile, the present methods of preparation of food, both in the home and before it arrives there, deplete the protective potassium.

Mechanisms of Hypertension (High Sodium-Low Potassium Diet)

The hypothesis we propose to explore is that excessive consumption of dietary sodium chloride, coupled with diminishing dietary potassium (the "high sodium-low potassium environment"), induces an increase in the extracellular fluid volume that in turn, among those with appropriate genetic propensity for it, brings

on hypertension. Data from animal models, studies of physiologic systems interactions, studies of populations and evidence of the therapeutic efficacy of both low sodium-high potassium diets and the therapeutic efficacy of saluretic diuretic agents overwhelmingly support this hypothesis.

Guyton and his co-workers[1,5,20,21] have been the principal developers of the systems analysis approach to an understanding of the control of arterial pressure and hypertension. Page[22] considers hypertension a mosaic. Guyton's analysis in a sense describes the tesserae, assesses a magnitude of influence for each and tells how it contributes to the realization of the cartoon. We are convinced of the validity of Guyton's systems analysis approach to the control of arterial pressure. However, our objective in this review is somewhat to one side of this elegant explication of mechanism. That analysis, insofar as it concerns itself with the role of sodium and potassium, and indeed it does so centrally, addresses the endogenous metabolism of these elements. We are concerned herein much more with the exogenous aspect of the role of sodium and potassium in hypertension. Before taking a hard look at what goes on "outside," however, it is crucial to document what goes on "inside," or the examination of the human dietary intake of sodium and potassium would be an academic exercise deserving little attention.

Coleman et al.[1] comment that one of the animal models of hypertension is ". . . salt induced hypertension, where excessive salt is combined with reduced renal function . . ." We must take some issue with that statement, specifically with the word *reduced*. Now Guyton's group work primarily with dogs and we work mostly with rats. It is true that it is almost impossible to induce hypertension with sodium chloride in the dog[23] unless one does "reduce" renal function.[24] Not so in the Sprague-Dawley rat. The majority of these animals will manifest hypertension with any intake of salt much in excess of that of the Hubbel-Mandel-Wakeman mineral mix[25] fed at the 3 percent level. That 3 percent is for *all* the mineral mix; the sodium allowance is 0.14 percent (expressed as NaCl) in the final diet. Ordinary "laboratory chow" contains seven times or more as much sodium chloride as that—1 percent or higher. Laboratory chow *is* a high sodium diet. Later in this review, we will develop and document the thesis that hypertension is only one of the manifestations of the chronic toxic effects of excessive sodium chloride ingestion and not necessarily the most lethal one. So, it is important at the outset to grasp the fact that many experiments upon the "effect of" this and that have been, in fact, experiments upon the effects of a relatively high salt diet *and* this or that.

The evidence that standard laboratory rat chow is a high salt diet is simple and direct. Rats eating it manifest fully suppressed aldosterone secretion[26]; when they eat a diet with a lower sodium content, aldosterone secretion increases briskly in a very few days.

There is a general conviction, without much evidence to support it, that a saluretic diuretic regimen is "just as good" as a low sodium-high potassium regimen in the management of hypertension, although there is no evidence that any mechanism other than reduction of extracellular fluid volume is involved in either case. The sad fact is that a low sodium diet is difficult to obtain and maintain in a day of "convenience" foods and the high sodium-low potassium customs that characterize American cookery. However, it would be difficult to defend the thesis that the cause of hypertension in 23 million Americans is their failure to take saluretic diuretic pills several times a day throughout life.

We know little about the lifetime toxicity of antihypertensive drugs. Even those who are now engaged in therapeutic trials of medications in children prone to hypertension[28] express some concern that the implications of success in their trials might commit the child to a lifetime of pill-taking with unknown consequences in long-term toxicity. One might well ask: Are we permanently committed to the high sodium-low potassium environment? Can we devise a strategy to get out of it? It does not seem sensible to continue indefinitely to consume a seriously suboptimal dietary mix of sodium and potassium, which is toxic for many. An optimal mix might have as much to offer for longevity in humans as it clearly does in the rat.[27,29] A carefully controlled study in a population of young people prone to hypertension might shed important light on this vexing question. For the practicing physician, a tool whereby he could effectively identify those for whom the active prophylaxis of hypertension is indicated would be worthwhile. Such an objective indicator could warrant the trouble and vexations of maintaining a low sodium-high potassium intake throughout life.

Usual *Versus* "Normal" Arterial Pressure

It is possible that the "accepted norms" may be the usual pressures observed in the American population rather than normal pressures for *homo sapiens recens*. Blood pressures far lower than those found after age 50 among men and women in the United States[30] have been found in the 6th, 7th and even the 8th decades of life in Mayan Indians,[31] Andes natives,[32] Cook Island Polynesians,[33] African bushmen,[34] clerks in Calcutta,[35] female rural Northern Indians,[36] German contemplative monks,[37] Kenyan Samburu elders,[38] Buddhist farmers in Thailand,[39] Japanese farmers of the Tottori culture,[40] New Guinea natives,[41] Masai warriors,[42] Somali nomads,[43] Eskimos,[44,45] American doctors and nurses moving to China in the 1920's,[46–48] U. S. naval aviators,[49] inhabitants of Norielsk, a Russian Arctic industrial city,[50] and isolated Navajos.[51] In most of these populations, blood pressure remains at a level characteristic of persons in the United States at about age 25, increasing little if at all with advancing age. In many of the populations, the data may have been collected in a less than rigorously controlled manner. Nevertheless, it has been pointed out that it is not likely that the observers measured the arterial pressure accurately in the young while progressively and systematically underestimating the blood pressures in older subjects.[52] Newer reports continue to provide instances of populations whose systolic blood pressure remains below 120, 125 or 130 mm Hg throughout adult life.[52a–52d] One cannot, therefore, dismiss the possibility that the American data on blood pressure reflect merely usual, not normal, levels.

Vascular Hyperreactivity

Mendlowitz[7] has reviewed the role of vascular reactivity in systemic arterial hypertension and summarized the extensive contributions he and his associates have made. He concludes that "In most systemic vascular beds and in the systemic circulation as a whole, vascular reactivity to vasoactive substances acting directly or indirectly on the sympathetic neural and vascular receptor complex is increased in hereditary essential hypertension." Further, he states, "... such increased reactivity is present early in the course of the disease and even in essential prehypertension ..." Our own interest in this centers on the isolation and characterization of a humoral factor present in hypertensive patients and salt-eating hypertensive rats that sensitizes bioassay animals to exogenous norepinephrine.[53]

Sensitizing Factor to Catecholamines

Lately there has been a renewed interest in a "sensitizing factor" to catecholamines in hypertension, but because of the diverse results of both older and newer studies and the frequent utilization of inadequate controls, reports have been conflicting.[7,54–65] Several investigators have found evidence for a vasopressor agent potentiating factor among hypertensive subjects,[60,66–68] and a transmissible humoral factor has been suggested by a study by Dahl et al.[69] utilizing the parabiotic union of a strain of rats genetically susceptible to the development of hypertension.

Recently, studies by Mizukoshi and Michelakis[70] and from our laboratories[53] resulted in reports of a significant increase in vasopressor sensitivity to norepinephrine and angiotensin after the administration of small quantities of serum from hypertensive humans or animals to bioassay animals. This increase was thought to be due to a heat-stable, nondialyzable substance that was produced and released by the ischemic kidneys of patients with renovascular hypertension. It was also found in the plasma of patients with essential and malignant hypertension and some normotensive subjects. Sodium restriction in these hypertensive subjects unequivocally reduced the plasma activity of this substance.

Spectrums of Susceptibility in Hypertension

An important feature of hypertension is that there is a considerable spectrum both in "susceptibility" to it and in the degree of end organ damage and its rate of occurrence among those who have it. Sex and race differences are influential in this regard as to group effects, but there is a large individual variation within any age/sex/race cell we are able to define.

Animal experimental work may well shed light on this issue. Two kinds will be cited. In rats of the Sprague-Dawley derivation, intermediate levels of salt feeding, corresponding perhaps to a human intake of 14 to 28 g/day with other dietary constituents held constant, reliably produces hypertension (Fig. 1A). If a similar sodium chloride intake is provided but extra potassium chloride is also fed throughout life, a dramatic

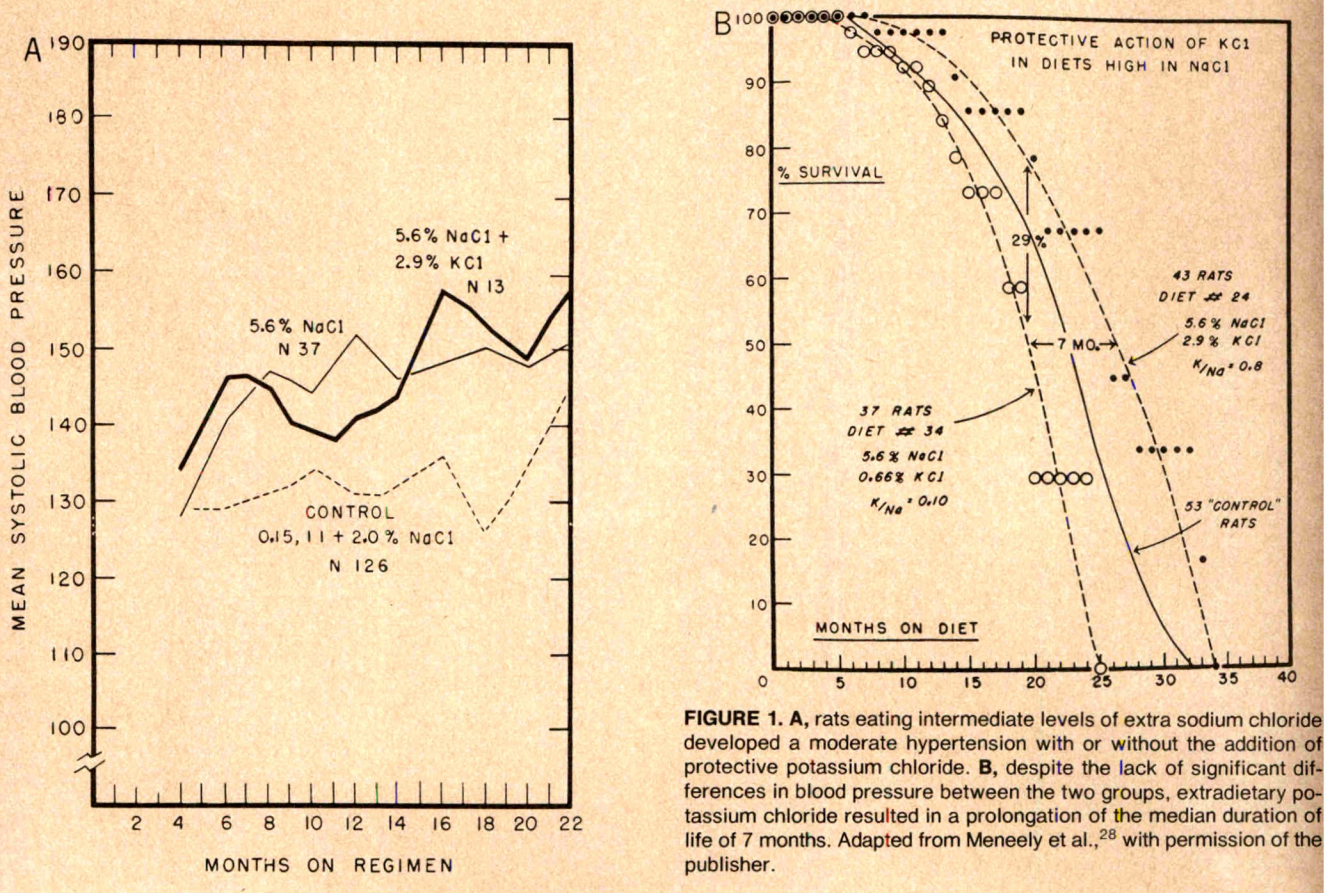


FIGURE 1. A, rats eating intermediate levels of extra sodium chloride developed a moderate hypertension with or without the addition of protective potassium chloride. **B,** despite the lack of significant differences in blood pressure between the two groups, extradietary potassium chloride resulted in a prolongation of the median duration of life of 7 months. Adapted from Meneely et al.,[28] with permission of the publisher.

effect is demonstrated. The level of blood pressure manifested by these rats is not significantly lower than among those not receiving extra potassium, but there is a very large increase in the median duration of life, from 19 to 26 months.[28] Such a 7 month difference represents a very long time in the life of a rat, equivalent perhaps to 21 years for human beings.

Figure 1B presents a composite of two separate experiments, a "pilot" study of 13 rats and a follow-up study of 30 rats, each with concurrent groups of "unprotected" rats, 7 in the first case and 30 in the second. An almost identical experiment performed later produced similar results.[71,72] Note that the 43 rats protected with potassium chloride also outlived the controls. We think that our control diet may have been suboptimal in some way. Perhaps 1.1 and 2.0 percent sodium chloride diets are life-shortening without being severely hypertensigenic. Evidence earlier cited[26] indicates that 1 percent sodium chloride is excessive in that it fully suppresses aldosterone secretion. The experience of Dahl et al.[73,74] and of others[75–78] confirms a dissociation between hypertension and other noxious effects of excess dietary sodium chloride. These data have not impressed some experienced workers,[79] but they nevertheless suggest that a similar circumstance could obtain in man, namely, that the level of blood pressure may not always be an adequate indicator of the seriousness of the underlying disorder or of the rate at which it is progressing.

Another set of animal experiments with similar implications has been reported by Aoki and Okamoto et al.[75,80,81] They were able to breed strains of rats so that when two propensities were compared—high and low susceptibility to elevated blood pressure and high and low susceptibility to the development of cardiovascular lesions—substrains were distributed in all four cells of the four-fold comparison table.[75] Most important is the finding that some strains with high susceptibility to cardiovascular lesions had low susceptibility to high blood pressure and some strains with high susceptibility to elevated blood pressure had low susceptibility to cardiovascular lesions. More recently, these workers[82,83] have bred strains with special susceptibility to stroke. They report that increasing the intake of salt ". . . increased [the blood pressure], and the onset of stroke markedly accelerated in all groups of spontaneously hypertensive rats." It is trite to say that observations in other species cannot be transferred to man, but it would be unwise to overlook the possibility that manifestations observed in lower animals might also be manifest in man.

A Mosaic Disorder With a Final Common Pathway?

Page's apt expression, ". . . the regulatory mosaic that determines the level of blood pressure," [22] is in some danger of becoming a hackneyed phrase through frequent reference, but that does not make the concept less valid. In the late stages of hypertensive cardiovascular disease, it is not difficult to suspect that there is a "final common pathway." Anatomically, the manifestation is arteriolar muscular hypertrophy and narrowing with extensive parenchymal damage downstream owing to local ischemia. Laragh et al.[84,85] and others[86–98] have collected some good physiologic evidence to suggest that the full-blown and rapidly progressive "malignant" phase of hypertensive cardiovascular disease is largely a renin-angiotensin-mineralocorticoid–mediated disorder. However, some findings in malignant hypertension are difficult to reconcile with this formulation.[99,100] Those of us who have worked much with hypertensive rats, in which the natural history of hypertension is much shortened compared with its slow evolution in man, have come to learn that, when the systolic arterial pressure reaches a high level, say about 200 mm Hg, something new happens. The rat's condition begins to deteriorate rapidly and, at autopsy, extensive necrotizing arteriolar disease is evident. The late Ernest Goodpasture, dean of anatomic pathologists of his day, considered these changes morphologically identical with the findings in human "malignant" hypertension.[101]

In most human victims of essential hypertension, the malignant phase is not manifested. At first scrutiny, the conditions appear to follow the previously mentioned "final common pathway"—widespread arteriolar disease without arteriolar necrosis but with widespread resultant tissue damage evident most frequently in the brain, eye, heart, kidney or combinations thereof. A variable degree of atherosclerosis is usually admixed so that end-stage hypertensive cardiovascular disease is truly a complex clinical disorder.

It now begins to appear that the concept of the "final common pathway" may be misleading. Although generally valid as a clinical epitomization, it diverts attention from several sets of observations suggesting that elevated blood pressure may not occupy the position of primacy we now assign it. The previously discussed rat strains of Aoki and Okamoto and their co-workers[75,80–83] suggest that the propensity for elevated blood pressure, development of cardiovascular lesions and stroke may each have a different genetic basis. One of us knew for a long time a professional colleague who had six siblings that died of a cerebrovascular accident. His logical apprehension later proved justified when he became the seventh victim. Irrespective of genetics, it now appears that a biochemical agent—angiotensin, for example—can have a direct effect upon myocardial protein synthesis and cardiovascular hypertrophy other than by way of increased heart work load in hypertension.[77] Oparil et al.[78] using nerve growth factor antiserum in spontaneously hypertensive strains of rats have accumulated evidence that left ventricular hypertrophy in hypertension may be independent of blood pressure level. They speculate that the hypertensive syndrome may really be a general cardiovascular myopathy in which hypertension is merely epiphenomenal. It has long been known that repeated injections of norepinephrine can produce elevation of blood pressure that will persist after the injections are stopped. Now it has been learned that norepinephrine administered at subhypertensive levels can produce cardiac hypertrophy.[102] However, whatever its weakness, the concept of elevated blood pressure is still the major handle by which we must attempt to grasp this matter.

Genetic and Conditional Genetic Susceptibility

There is a large body of clinical and experimental evidence that essential hypertension has a genetic component.[73,74] The condition has been thought to be transmitted by a dominant gene or genes. It is far from clear whether a single gene with incomplete penetrance or several genes might be involved,[103] but the issue is clouded by the fact that children, in the words of Edwin

Grant Conklin, also "inherit their environment," physical, psychic and socioeconomic. There is, however, no question that hypertension "runs in families."

Another facet of the problem is that, to judge from animal models, many forms of hypertension are genetic in origin but only in a conditional sense. Thus, Dahl's strain of "sensitive" rats only became hypertensive if they received more sodium chloride than required for normal growth and development.[73,74] Oparil et al.[78] showed that preventing the ingrowth of sympathetic nerves to the kidney prevents hypertension but not cardiac hypertrophy in the spontaneously hypertensive rat.[78] Others have produced convincing evidence that sympathetic nervous overactivity is the essential factor in the development of hypertension in the "spontaneously" hypertensive rats of the Okamoto strain.[75,80,81,104,105] Although many similar observations could be cited, these suffice to show that a person susceptible to hypertension may never manifest it because the noxious agent or agents upon which hypertension is conditional in his case may not come into play.

The Tracking Phenomenon

Among children a "tracking phenomenon" occurs that persists into adulthood; that is, position above or below the mean in the blood pressure array tends to be maintained.[106–108] We have reported the same observation in rats.[17] In addition, in lifetime studies of colonies of hypertensive rats, positions in the extremes of the arrays (plus or minus 1 or 2 standard deviations) proved to be reliable predictors of the likelihood or unlikelihood that other effects would be manifested later in life, such as electrocardiographic abnormalities characteristic of hypertensive cardiovascular disease, increased blood cholesterol or shortened life span.[109]

Much less obvious is the established fact that most, if not all, forms of hypertension, become self-sustaining once initiated. This has been seen in many animal models. For example, Tobian et al.[110] and Dahl[111] found that salt-induced hypertension could persist after excess salt was withdrawn. There are two implications in this fact. The first is that the causative agent or agents in a given instance of hypertension, or even in a given subject who is going to become hypertensive, may play its evil role and then leave the scene. The scenario thereafter may never be the same. The second implication is that it may be crucially important in a specific person to detect the noxious agent or agents upon which his hypertension is conditional and remove them as early as possible. This last relates to another observation in animal models, namely, that if the noxious agent acts for a long time the resultant hypertension becomes self-sustaining and is irreversible, whereas if the noxious factor has been at work for only a short time the hypertension induced by it is not self-sustaining and usually can be reversed by removal of the noxious influence.

Dietary Sodium and Potassium

Present knowledge of sodium and potassium nutrition[112] derives in large part from a better understanding of the role these two elements play in the body. Apparent contradictions that have led to confusion and controversy can now be understood in the light of recent advances in genetics.

Discovered by Davy in 1807 with use of electrolysis, potassium,[113] and sodium[114] are essential for normal growth and existence. Extremes of intake can vary the potassium:sodium ratio in the bodies of mice from 1.5 to 2.4, and experiments with dogs yield similar results.[115] The important facts concerning the absorption and excretion of sodium and potassium were first published by Salkowski[116] in 1871. An interrelation between dietary sodium and potassium has been known since the time of von Bunge[117] and explored more recently by Miller.[118,119] The maximal and minimal limits for sodium and potassium intake are interdependent and also vary with water intake and the efficiency of the kidney. The desirable upper limit for sodium intake is controversial. Present evidence indicates that 10 to 60 mEq of sodium, 0.6 to 3.5 g/day as sodium chloride, is an adequate intake for an adult man. Potassium is plentiful in naturally occurring foods. The ordinary diet supplies from 50 to 100 mEq, 3.7 to 7.4 g/day as potassium chloride, provided that it is not leached out in processing or cooking food.

Physiology of Sodium and Potassium

There is reason to believe that, early in the evolution of life on earth, the potassium content of the Precambrian seas was much higher with respect to the sodium concentration than later came to be the case.[120] This is adduced as a reason why potassium is the principal intracellular electrolyte. At the time of "emergence from the sea," sodium concentration in the sea had become relatively high. This latter is thought to be the basis for the electrolyte pattern of the extracellular compartment, with its relatively much higher concentration of sodium.

Intra- and extracellular osmolarity: Sodium and potassium are important contributors to intra- and extracellular osmolarity. Mammalian interstitial fluid is an almost protein-free filtrate containing sodium as its chief cation. Under steady state conditions, this solution is in equilibrium with the intracellular environment, that is, the effective osmotic pressures of the two compartments are equal because the cell membrane is freely permeable to water. The intracellular fluid, more complex, has several chief contributors to its osmotic pressure: calcium, magnesium, protein, phosphate and potassium. A significant number of these intracellular ions are not present as osmotically active substances but are sequestered by various structures within the cell and are regulated by and regulators of cell activity.

Cells have no mechanism for directly controlling their own individual osmotic pressure. They rely upon the osmotic control of the extracellular fluid. Any substantial departure from normal intracellular fluid osmotic pressure cannot be tolerated by the organism. The osmotic pressure of the extracellular fluid is closely regulated by one of the most complex homeostatic devices.

Electrogenic pump: Sodium and potassium are also involved in the electrophysiology of cells. Early studies[121,122] revealed that the permeability characteristics of cell membranes are not sufficient to account for the disparity in the composition of fluids inside and outside the cells. It is necessary to postulate the existence of an "electrogenic pump." This pump is energy-dependent, deriving its energy from the metabolic processes of the cell.[123] It transports sodium from the intracellular compartment to the extracellular fluid and potassium into the interior of the cell. The two ions are

transported in a loosely coupled manner.[124] The diffusion properties of each of the two ions with respect to the cell membrane is such that a membrane potential is generated by the diffusion of potassium down its electrochemical gradient, leaving a net intracellular negative charge.[123] This electrogenic pump has been shown to be sensitive to intracellular sodium concentration and extracellular potassium concentration. Increases in either or both concentrations increase the rate of the pump.[124] The result is a pump with its own system of feedback control related directly to the concentration of the transported substances. Changes in the permeability of the cell membrane can lead to marked changes in the cell's membrane potential. The diffusion of sodium and potassium down their electrochemical gradients after a change in permeability is the factor responsible for the genesis of the propagated action potential observed in excitable tissues.[123]

Homeostatic mechanisms: Sodium and potassium are also indispensable components of the homeostatic machinery of the whole organism. Both ions are integral parts of the control mechanism of acid-base balance, renal tubular sodium and potassium being appropriately exchanged for hydrogen ions or reabsorbed depending upon the needs of the organism. Also, the ions are intimately involved in the regulation of extracellular fluid volume and the maintenance of blood pressure. Small sustained changes in the sodium concentration of the extracellular fluid can have profound effects upon arterial blood pressures.[125] Small changes in blood potassium concentration have a profound effect on cardiac performance. The ions are likewise involved in carbohydrate metabolism in that the active transport of glucose across the intestinal mucosa requires the movement of sodium in the same direction,[126] the peripheral uptake of glucose by cells is associated with a shift of potassium from the extracellular fluid into cells, and some enzymes of glycolysis and oxidative phosphorylation are potassium-dependent.[127] Potassium depletion also inhibits the secretion of insulin by pancreatic islet cells in response to a hyperglycemic stimulus. Protein and amino acid metabolism are likewise affected by these two electrolytes.[126]

Because of the profound influences that even subtle changes in sodium and potassium balance have upon cell metabolism and the organism, it is not surprising to find that amazingly complex systems have evolved to maintain the balance of these electrolytes within critical tolerances. The importance of this balance is underscored by the redundance of controls that have developed. A failure in any one component of this control system can often be compensated for by the remaining parts so that the organism does not perish.

Sodium and Potassium Nutrition

It still seems incredible to some, despite a massive body of evidence, that common table salt might be noxious. Since its effects are insidious, it has been difficult to document its toxicity in man, especially since genetic differences in sensitivity abound and make the data from population surveys bewildering. The matter is also complicated by the protective effect of dietary potassium.[28,128]

Dietary salt in hypertension: A unifying and simplifying theory is needed. It is obvious that sodium chloride increases blood pressure in some[129,130] and does not in others[131,132] and equally obvious that restriction of dietary sodium reduces high blood pressure in some and not in others.[133–135] The genetic explanation of this has already been noted and will be reviewed later. Because excess sodium does not increase the blood pressure of all persons, some conclude that it does not increase anyone's blood pressure. Because sodium restriction does not reduce the blood pressure in all hypertensive subjects, some conclude that it is not worth restricting sodium in any hypertensive subject. Saluretic diuretic agents reduce blood pressure in most patients with hypertension. It has been shown that patients with "essential" hypertension who respond to diuretic drugs respond equally well to low sodium diets.[136,137] Dustan et al.[138] state, "In this culture, therapeutic low sodium diets have little place in the treatment of hypertension when renal function is good enough to allow diuretic drugs to have an effect." This probably states the consensus for American clinicians. Like many published statements, it is both right and wrong. Right, because in the American high sodium-low potassium environment it is extremely difficult to keep a patient on a daily diet of 0.5 or less of salt, and such a diet is difficult to purchase. However, the statement is also wrong for several reasons. For many patients such severe restrictions are not necessary.[137] More important, Dustan's statement assumes that we are locked into the high sodium-low potassium environment and will do nothing about it. This may well be correct, for human inertia and habit are formidable antagonists. Here we do not have a conspiracy of silence; we have a counsel of despair. The heavy use of salt by the food industry as well as in the home and the growing trend toward leaching out potassium involves so many people and so much custom that most physicians simply throw up their hands and settle for some such noncontroversial advice as, "take it easy with the salt . . ." Moreover, commercial factors are at play. Sodium salts are usually cheaper than the foods to which they are added. Since salt is hygroscopic, salted foods hold weight better and so yield more profit per kilogram. Highly salted foods "keep" better. Shubsachs,[139] writing to Lancet, complains that commerce prefers the cheaper Chile saltpeter ($NaNO_3$) to true saltpeter (KNO_3) for the preservation of foods. He has a point. Less defensible is the attitude of the medical profession. Although low salt diets are obviously effective in hypertension,[133–138] it would appear that physicians would rather prescribe pills than diets. Osler[140] noted, "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals."

The unifying and simplifying thesis we wish to affirm is that excessive dietary sodium chloride is in itself noxious, that potassium has a protective effect against chronic sodium toxicity and that genetic factors underlie all responses to excess sodium intake.

Sodium Chloride, a Condiment, Not a Requirement

Most human beings have a taste for salt, but there is good evidence that this is due to its properties as a condiment rather than to some mysterious physiologic need. Lapicque[141] contributed an invaluable anthropologic observation concerning a tribe in Africa that lixiviated a salt from the ashes of certain plants. Analysis showed it to be a fairly pure potassium chloride.

Sodium chloride was available and cheap in the area inhabited by this vegetarian people, but they used it only when their own potassium chloride was scarce. Even then, they would mix it with a little potassium chloride. Lapicque thus convincingly documented the use of salt purely as a condiment, similar to the use of pepper, curry powder, paprika (capsicum), pimento and numerous other widely used flavorings. Sodium is readily available in nature away from the sea, potassium is not.[142] The lixivium from most plant ashes is rich in potassium carbonate which, because of its disagreeable taste, earned the name "salt of wormwood." It was a pure fluke that Lapicque's inhabitants of the basins of the Ogooue and the Sangha "by the unconscious experimentation of successive generations" came upon a particular species of plant whose ashes yielded a nearly pure potassium chloride with a good sharp saline taste. Lapicque points out the extraordinary ability of human beings, by just such experimentation, to identify other gratifying substances of widely differing plant origins. Thus, caffeine was found by the Abyssinians and the Arabians in coffee, by the Chinese in tea, by the Paraguyans in maté and by the natives of the Amazon region in guarana. Lapicque thus effectively disproved von Bunge's thesis[143] that a vegetarian diet required extra sodium chloride. We found some years ago that potassium chloride could be admixed with sodium chloride to a considerable extent, up to 50 percent for some people, without a noticeable change in taste,[144] and Frank and Mickelsen[145] recently made similar observations. A product with this mixture has recently appeared on the open market. Tobian[29] ends his scholarly review with the statement, "An alteration of the amounts of sodium and potassium in the diet of populations susceptible to hypertension may be the most practical way to decrease the incidence of the disease."

Kaunitz[146] also marshals the evidence against von Bunge's views and laments that these are still widely quoted. He goes on, however, to argue that extra salt may be "correlated with emotional stimulation . . . that it may be consciously or unconsciously pleasurable . . . as a causal factor in the craving for salt." We know of no evidence to support Kaunitz's speculation, but it is an interesting one. Could it have a stimulating effect on the sympathetic nervous system? The latter is clearly involved in some way in "essential" hypertension.

Salt and Evolution

Physiophyly concerns the evolution of bodily functions as morphogensis concerns the evolution of form. It takes time for a new or altered function to evolve. Life began 2 billion years ago, emergence from the sea was 360 million years ago, man-like creatures came into being 2 million years ago. By then, many physiologic mechanisms were firmly encoded in the genes. Dahl and Meneely[147,148] pointed out that a primal herbivorous people probably consumed at the most 10 mEq/day of sodium, 0.6 g as sodium chloride. A strictly carnivorous man requiring 4,000 kilocalories might have consumed 60 mEq (3.5 g as NaCl) on successful hunting days.

TABLE I

Sodium and Potassium in a 100 g Serving of Peas

	Sodium		Potassium	
	mEq	as NaCl (g)	mEq	as KCl (g)
Fresh peas	0.04	0.002	9.72	0.725
Frozen peas	4.35	0.254	4.09	0.305
Canned peas, liquid poured off	10.00	0.585	4.60	0.343
Add salt, serve with salted butter	?	?	?	?

Now, for a mere 2,000 years or less, "civilized" man has added 6 to 18 g/day of sodium chloride to his food. There has hardly been enough time for the genetic material to alter in a favorable adaptation. The dog evolves more rapidly; perhaps that is why it can eat a salty diet with apparent impunity.

Aside from the rather uncertain matter of treks to salt licks, no terrestial mammals except man add salt to their food. Although it now appears that the minimal adult daily requirement for sodium is approximately a few hundred milligrams or so[147]—surely no more than a gram—the average daily consumption of this substance is from 10 to 35 times this amount among most "civilized" people. Most reference works cite the Food and Nutrition Board Recommended Dietary Allowance NAS-NRC of 1 gram of dietary sodium chloride per kilogram of water intake (in fluid and food). Water consumption is actually a function of the amount of salt in the diet, as noted by Pliny the Elder.[149] In the experimental animal, water consumption varies directly with dietary sodium chloride.[150] Since the average daily turnover of water is about 2,750 ml for an adult weighing 70 kg, this recommendation would suggest about 3 g/day of sodium chloride. Much evidence indicates that this is more than enough.

The High Sodium-Low Potassium Environment

No mammals other than man cook food. Let us briefly trace the changes in sodium and potassium in a common food to exemplify the extent to which potassium is depleted and sodium increased. Table I shows the data for a 100 g serving of peas.

Canned peas, drained and before butter and salt are added for serving at table, thus contain 250 times as much sodium as the fresh product and more than half of the potassium is gone.[151,152] The increased demand for canned and convenience foods is attributed to the phenomenal increase of the small apartment and part-time housewife. Intake of sodium is thereby greatly increased and that of potassium reduced. Some other convenience foods show an even greater rearrangement of elemental composition (Table II).[153]

Thus, urbanization of the population together with ever increasing use of convenience foods further contributes to the high sodium-low potassium environment. It is also unfortunate that the processing of foods, which so greatly increases sodium content, usually depletes the protective potassium.

TABLE II

Sodium and Potassium in a 100 g Edible Portion of Common Foods

	Sodium		Potassium	
	mEq	as NaCl (g)	mEq	as KCl (g)
Olives	104.4	6.10	1.41	0.11
White bread	22.0	1.29	2.69	0.20
Cornflakes	28.7	1.68	4.09	0.31
Cheddar cheese	30.4	1.78	2.10	0.16
Dried nonfat milk	22.8	1.33	34.1	2.54
Bacon	77.0	4.50	5.75	0.43
Chipped beef	187.0	10.94	5.12	0.38
Smoked ham, raw	110.0	6.44	6.34	0.47
Frankfurter	47.8	2.80	5.88	0.44
Salami	54.8	3.21	7.72	0.58
Canned crab meat	43.5	2.54	2.81	0.21
Canned salmon	23.5	1.37	8.44	0.63

Although consumer purchase of table salt has declined slightly, salt in processed and prepared foods has increased. Sodium intake is increasingly determined by food processors rather than by the individual consumer.[154] Salt is, of course, a preservative because it is toxic for microorganisms. A generous addition increases the keeping quality of food products. Many convenience foods now tast saltier than would be the preference of the buyer. In turn, this influences national taste.

Taste for Salt

Dahl[147] found, in patients consuming long-term diets containing up to 250 mg/day of sodium chloride, that the addition of 1 g to their daily intake evoked comment although rapid adaptation occurred. In sharp contrast, among the subjects consuming 10 to 20 g/day the addition of 5 or 10 g could go unnoticed. It was concluded that salt appetite is induced rather than innate and that, like salt intake, appetite for salt bears no necessary relation to requirement. Wotman et al.[155] confirmed an elevated salt taste threshold as characteristic of patients with hypertension. The salt preference of animals may represent an effort to maintain sodium homeostasis[156,157] since sodium is scarce in nature away from the sea,[142] whereas salt appetite is acquired by human beings primarily as a result of social and dietary custom and usage.[147,148] Schechter et al.[158] found no difference in taste thresholds between hypertensive and normotensive subjects but, when offered distilled water or saline solution by free choice, the hypertensive patients consumed more than four times as much sodium chloride as did the normotensive volunteer control subjects.

Chronic Sodium Chloride Toxicity and the Protective Effect of Potassium

Chapman and Gibbons[159] in 1949 provided a superb portal to the past history of dietary sodium and potassium in a scholarly and exhaustive review. They noted the bibliographic contribution of Glatzel[160] in 1937 but considered it uncritical. They recognized the early 19th century "milk cure" of Christian[161] and Karrell[162] as the first therapeutic use of fluid and salt limitation, then traced development through Redtenbacher, Salkowski, von Koranyi, Carrion and Hallion, Achard and Loeper, Widal and Lemaierre, van den Bergh, Merklen, and Ambard and Beaujard.[163] In what Dahl called a "prophetic paper," Ambard and Beaujard in 1904 considered the possible role of salt as a cause of hypertension. Whatever the prophecy, the blood pressure in their patients tended to decrease when dietary salt was restricted, and to increase when more salt was allowed. Chapman and Gibbons trace the recognition of the role of sodium (and potassium) through Laufer, Bayer, Achard, Blum, Magnus-Levy and Allen[164–168] to what they considered the crucial experiment by Addison,[169] who found in 1928 that "potassium salt regularly produced a decline in blood pressure, while sodium salt just as regularly produced a rise." The work of Berghoff and Geraci[170] and Thompson and McQuarrie[171] followed. It was McQuarrie's fascinating observation that potassium reduced hypertensive blood pressure even though the dietary salt intake remained large;[172] this finding stimulated one of us and his colleagues[28] to add extra potassium to rat diets high in sodium content. We were unaware at that time of the 1931 work of Priddle.[173] Meara[174] in 1918 first suggested, in the United States, the limitation of salt in hypertension, but Allen[164–168] was really the initiator of the first wave of interest in low salt dietary therapy. Kempner[135] was responsible for the second great wave of salt restriction 25 years after Allen. Much of the clinical material in these early studies was really unsuitable for critical evaluation of the merit of salt restriction. With few exceptions, such as the study of Priddle,[173] increased potassium intake was not explored.

In the light of the convincing evidence Chapman and Gibbons had marshalled, Dahl[175] marveled: "For reasons that are difficult to fathom, there appeared a great deal of antipathy to Kempner's reports as well as irrational disbelief in the effectiveness of the diet. In a major review of the subject early in 1949 (Chapman and Gibbons) it was stated that suggestion had not been ruled out and that restriction of salt intake has not been conclusively shown to be independently capable of lowering the blood pressure in hypertensive patients.

Salt and Extracellular Fluid Volume

Chapman et al.[133] also pursued their own research on the topic. They clearly showed that the rice-fruit diet is needlessly deficient in protein, that it reduces blood pressure in some patients and that, when it does so, restriction of salt is the effective component. Although only a portion of their patients had a significant reduction in blood pressure, all had a reduction in extracellular fluid volume. Since then, many observers have noted that salt restriction decreases extracellular fluid volume. Dustan et al.[138] have pointed out that retention of as little as 20 mEq each day of sodium will add a liter of extracellular fluid each week. Systems analysis physiology of control of blood pressure[1,5,20,21,176] explains the portent of these seemingly small differences. The message is clear: Restriction of sodium intake reduced extracellular fluid. Blood pressure decreased toward normal in all of the patients of Chapman et al., but factors other than excess extracellular fluid supported the elevated blood pressure in some. To restate the message: One manifestation of excess dietary sodium chloride is expanded extracellular fluid volume. It is probable that many Americans have excessive extracellular fluid volumes due to excess dietary sodium intake.

Sodium Chloride and Hypertension

Genetic factors: Sodium in the diet in excess of need both does and does not cause hypertension. It depends upon who is eating the salt: Some persons are and some are not susceptible, and some persons will not become hypertensive under any but the most extraordinary circumstances. These statements are true of individual subjects and of whole populations, whether one is speaking of people or animals. The explanation lies in genetics. Clues to differences in susceptibility have been evident for many decades. More recently, animal studies have yielded good evidence to explain the pleomorphic human epidemiologic observations. Alexander et al.[177,178] may well have been the first (1954) to develop a "spontaneously" hypertensive animal, a strain of spontaneously hypertensive rabbits. Dahl and Schackow[179] credit Smirk and his group[180–182] with the first report of a colony of rats with genetically determined elevations of blood pressure. In 1962, a sodium chloride-sensitive strain of rats was developed by Dahl et al.[73,74] In 1963, Okamoto and Aoki et al.[75,80–83] isolated a Wistar-derived strain of spontaneously hypertensive rats. Louis et al.[183] found that this strain became hypertensive with a decreased salt intake and further explored the genetic component.[184] Hypertension in all these "spontaneously" hypertensive animals is brought on earlier and made much worse by extra dietary sodium chloride.[83] Meanwhile Schlager and Weibust[185–187] found that variations of blood pressure among mice was genetically determined and concluded that several genes were involved. An important paper by Aoki et al.[75] sheds a good deal of light. Their careful analysis of substrains of their hypertensive rats showed genetic independence of "sensitivity" to salt —that is, its propensity to induce hypertension—and of "toxicity," by which they mean the propensity of salt to induce vascular lesions and to accelerate mortality. They present a fourfold genetic categorization: high sensitivity, high toxicity; high sensitivity, low toxicity; low sensitivity, high toxicity, and low sensitivity, low toxicity.

Dahl et al.[73,74] found that long-term consumption of excess sodium chloride may induce pathologic lesions without direct relation to blood pressure. As noted earlier, we found large differences in the median duration of life in our rats without significant differences in blood pressure.[27] Dahl et al.[73] note that they have repeatedly seen lessening of vascular disease, clearing of retinopathy, for example, even when the patient's pressure failed to decrease with a low salt diet. Kempner[76] reported the same finding earlier. Still more recently Okamoto and coworkers[82,83] explored the effect of extra sodium chloride on the genetic susceptibility to stroke in their hypertensive rats. Thus, there is both animal and human evidence that elevation of blood pressure is not the only toxic effect of excess sodium chloride. Studies in animals and clinical observation in humans reveal a genetic dissociation of several independent noxious effects.

A spate of papers have appeared for and against the role of sodium chloride in hypertension. Chapman and Gibbons[159] credited Allbutt,[188] Huchard[189] and Von Basch[190] as those "whose combined efforts delineated essential hypertension as a separate disease entity . . ." They erred because hypertension, essential or otherwise, is neither a disease nor an entity. It is a clinical physiologic observation. Even today, the many mechanisms involved in high blood pressure are only partially understood and then only in the framework of systems analysis physiology. Blood pressure is the result of an exceedingly complex interplay of multiple hereditary, constitutional and environmental factors. Once hypertension is initiated, it can become self-perpetuating even though the original "cause" is no longer present. Hypertension persists in our rats when excess dietary salt is withdrawn. Dahl[111] and Tobian et al.[110] have also made this observation.

Genetic factors explain why some human beings become hypertensive and some do not in otherwise exactly similar circumstances. Genetic factors coupled with dietary sodium and potassium account for most of the astonishing differences recorded in studies of populations. Henry and Cassel[52] have assembled in one place and presented in clear format most of the accumulated data on populations. However, the thesis they develop seems to us to be addressed to second and third order factors in blood pressure control. In a recent article dedicated to Dahl, Friedman and Iwai[191] showed that Dahl's salt-sensitive rats with a sodium chloride intake just below that which will induce hypertension of itself soon manifest hypertension when exposed to an approach-avoidance conflict. Thus, psychic stress is selectively efficacious in producing hypertension in genetically predisposed animals. Only people genetically equipped to do so become hypertensive with excess salt intake. If they are so equipped, they will flourish as normotensive away from excess salt but their blood pressures will increase if they are given excess salt.[192] Psychic stress may make matters worse.

Total body sodium and extracellular fluid volume: Many investigations[193,194] have failed to find an excess of total body sodium among hypertensive patients. In salt-sensitive rats, Dahl and Schackow[179] found, at a time when experimental hypertension was still rapidly evolving, no evidence of change in whole body content of sodium or of potassium. However, Meneely and co-workers[71,72] did find some increase in total body sodium but only at high levels of excess salt feeding thought to correspond to human intake of 35 g/day or more of sodium chloride.

The data are lacking to predict human extracellular fluid volume with precision. Methods to measure it are not reproducible within small limits. Analysis of the blood pressure control system predicts that small changes in extracellular fluid volume would have significant hypertensive effects, changes approaching the error of measurement. Nevertheless, when the individual patient is used as his own control, suggestive changes may be detected. The finding of a reduction with a low salt diet has been discussed earlier.[133] The primacy of an increase of extracellular fluid due to increased ingestion of sodium chloride in the genesis of hypertension as hypothesized by Guyton and his associates[1,5] is now beginning to be well known.

Salt in Baby Food

Dahl[18] drew attention to the unenviable infant mortality rate in the United States,[195] believing that high sodium chloride levels in the infant diet were partly to blame. He pointed out that extra salt is neither necessary nor useful. Certain baby foods he tested in the late 1960's were lethal for rats because of their high sodium chloride content.[19] The Committee on Nutrition of the American Academy of Pediatrics concluded at that time that the salt intake of infants was several times larger than the requirement and recommended that the salt content of infant foods be reduced. Subsequent surveys have shown that manufacturers have complied.[196] However, some parents needlessly add salt to their infant's food in accordance with their own taste preference. This has the effect of giving unnecessary salt to the child and cultivating in him a taste for excess salt. Many parents are still not aware that the salt requirement of infants and children is low and that excesses are nox-

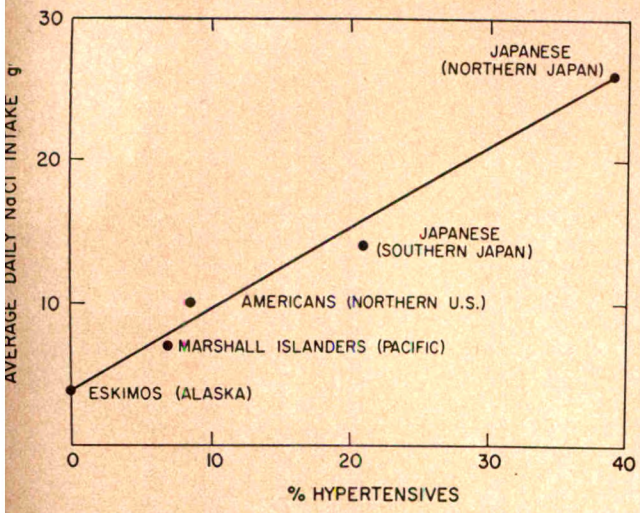


FIGURE 2. Sodium chloride intake and the incidence of hypertension in different populations. Adapted from Meneely and Dahl,[44] with permission of the publisher.

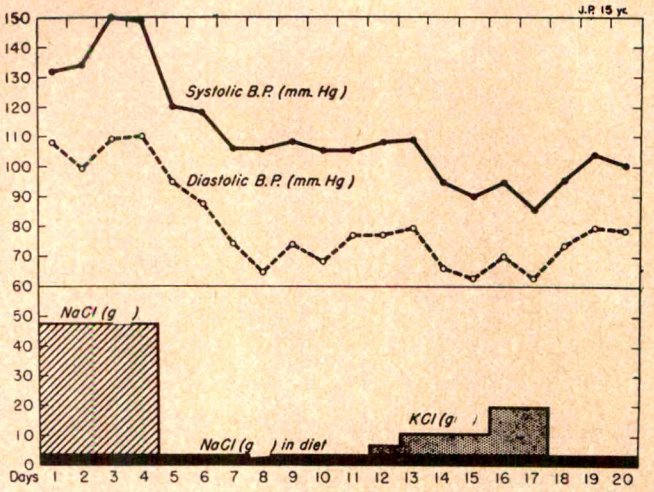


FIGURE 3. Hypertensigenic effect of sodium chloride and protective effect of potassium in a 15 year old salt-eating diabetic girl. B.P. = blood pressure. Reprinted from McQuarrie et al.[203] with permission of the publisher.

ous. The sodium content of human breast milk is very ow, 7.4 mEq/liter, less than 0.5 g as sodium chloride. It night be still lower if the mother restricted her salt in- ake.

Practical Considerations About Sodium and Potassium n Population Studies

There are many epidemiologic studies of salt intake n young people.[197,198] By and large they do not support he thesis that dietary sodium chloride alone is related o arterial blood pressure in any simple way. There are ome good reasons why our earlier stated thesis may still e correct despite the seeming negation of it by studies vithin populations. First, the dynamic range of sodium hloride intake in a given population is not likely to be arge enough to bring out a clear correlation. Second, in nost modern societies, the intake of sodium chloride reatly exceeds the requirements for it. Therefore, al- nost all persons susceptible to its noxious effects have lready been affected by it as much as they likely can e whereas those who are resistant to it will not show dverse effects even at high levels of consumption. If bout 20 to 25 percent of a population is destined to ecome hypertensive, this is still only one person in four r five. Anything other than a "large signal marker" vould easily be lost in the "noise" of the other 80 per- ent. When studies are made among different popula- ions, however, the correlation between salt intake and he incidence of clinically significant hypertension can learly be seen (Fig. 2).

Not everyone is as impressed with these data as are Meneely and the late Lewis Dahl,[44] who published hem. Langford and Watson[199] express skepticism and Henry and Cassel, arguing that sodium chloride intake 'can hardly be the initiating cause (of hypertension)," oint to the work of Sasaki,[40] who found low blood ressures in a Japanese population eating a generous ation of sodium chloride, about 14 to 15 g/day. They lid not note the earlier finding of Sasaki et al.[200] of low blood pressure in a population consuming large amounts of both sodium chloride and potassium. This highlights the third reason we think population studies may have been misleading, namely, lack of attention to potassium intake.

The ability of potassium in the short term to reduce blood pressure may be seen in Figure 3 from work by McQuarrie et al.[172] done in the 1930's. Although the patient's condition was not normal (she had diabetes) her blood pressure increased with excess ingestion of sodium chloride, was reduced after reduction of sodium chloride intake to about 4 g/day and was further reduced when she was given extra dietary potassium chloride. It also proves the point that it is not *always* necessary to reduce salt intake to milligram levels to reduce the level of the blood pressure.[137] Even more impressive is the case shown in Figure 4, also from McQuarrie et al. Extra potassium chloride produced an impressive reduction in blood pressure in spite of continued ingestion of excess dietary sodium chloride. Concurrent with these dramatic cardiovascular manifestations were some interesting changes in glucose metabolism. The interested reader should consult the original papers.[171,172] Figures 3 and 4 are from McQuarrie's address to the Minneapolis Hypertension Symposium,[203] where he chose to omit the glucose data.

The Sodium/Potassium Ratio Hypothesis

So far as we are able to learn, the concept of the sodium/potassium ratio was introduced in 1962 by Priddle[201] and discussed in an unsigned article in Nutrition Reviews[202] that same year. Langford and Watson[199] reported an experience with dietary sodium and hypertension which is common enough except that they went beyond their original negative findings: "We originally postulated that differing salt intake was the most likely variable to explain the blood pressure gradients we observed . . . We have now looked at the 24 hour Na excretion and blood pressure of over 600 individuals . . . In no case have we been able to find a significant positive correlation between blood pressure and Na excretion alone . . . ." Unlike many other workers, they subjected their data to further analysis. However, one of their findings is discouraging to the investigator embarking upon a similar study.

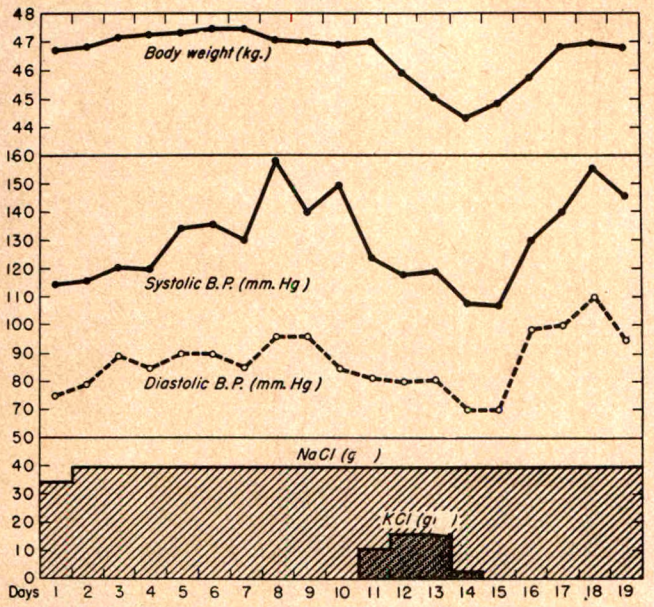


FIGURE 4. Dramatic effect of extra potassium on the sodium chloride induce hypertension of a 14 year old salt-eating diabetic patient. B.P. = blood pressure. (Adapted from McQuarrie et al.,[203] with permission of the publisher.)

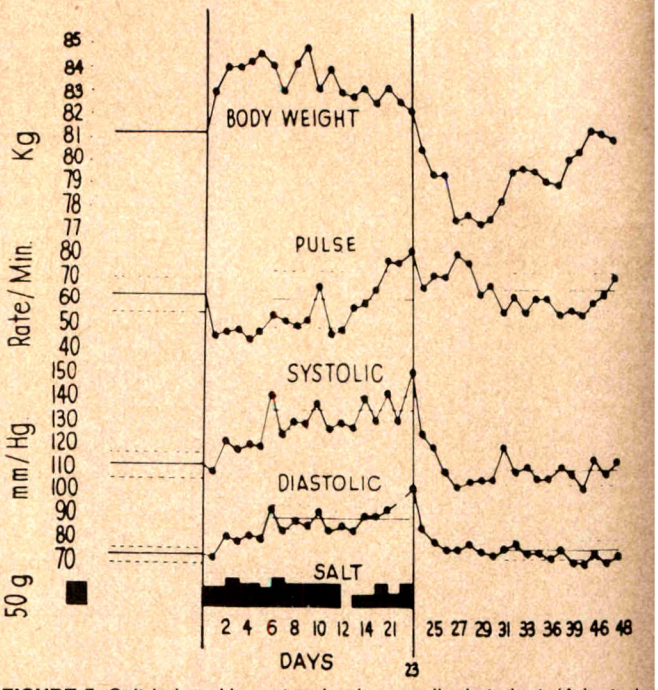


FIGURE 5. Salt-induced hypertension in a medical student. (Adapted from McDonough and Wilhelmj,[129] with permission of the publisher.)

Twenty-four hour collections of urine had correlation coefficients with 6 day collections of only 0.664 and 0.810 for sodium and potassium, respectively, and 3 day collections correlated only at the 0.900 and 0.941 levels with the sodium and potassium in 6 day collections. One is accustomed to feel some satisfaction with 24 hour urinary collections when the creatinine values are encouraging, but Langford and Watson's observation adds yet another word of caution to numerous personal communications concerning the variability of 24 hour sodium and potassium excretion.

Further analysis of their data did bring out one significant correlation, namely, the sodium/potassium ratio in 6 days of urine correlated positively with diastolic blood pressure observed over 8 days (no. = 101, $r = 0.372$, $P = 0.02$). In their report,[199] they present several reasons suggesting that this is more than a chance occurrence. It would be valuable if others with sodium and potassium urinary collection data would examine sodium/potassium ratios in relation to observed blood pressures.

The sodium/potassium ratio has clearly a worthwhile potential. We have argued earlier that failure to find correlations between dietary sodium and blood pressure in some population studies was possibly due to neglect of the potassium intake. Because of the saturation effect described later, however, this hypothesis must be interpreted with caution.

It may be of more than passing interest that those concerned with *diet* commonly use the potassium/sodium ratio because in virtually all naturally occurring items of diet, this ratio is larger than 1, sometimes as large as 1300 (fresh kidney beans, potassium mg/sodium mg). On the other hand, in *metabolic* work, sodium/potassium ratios are the rule because in collections of urine this ratio is almost always 1 or more and commonly ranges up to 10. This reversal epitomizes the difference, as far as sodium and potassium are concerned, between the amounts of these nutrients in food as the ingredients occur in nature and the reversal of the ratio in the actual diet of man. Dahl et al.[204] demonstrated in their salt-sensitive rats that the higher the sodium/potassium ratio of their food, holding sodium constant, the higher their blood pressure.

Saturation Effect

In this paper we have developed several lines of evidence to reconcile the findings in animal models and in some human experiments indicating the powerful hypertensigenic action of excess dietary sodium in people whose genetic material makes them susceptible to it, and to the remarkable protective effect of potassium against the toxic action of sodium. The patients of McQuarrie et al.[172] illustrate both points, but one may argue that these were not normal subjects. One experiment that has become a classic is the study that, with his teacher, John McDonough[129] performed upon himself when he was a medical student. In this perfectly normal young man, excess sodium chloride rapidly produced a brisk hypertension (Fig. 5).

In addition to McQuarrie, others have cited a favorable effect of extra potassium on blood pressure. Perhaps the earliest to do so was Addison,[169] who found in 1928 that "potassium salt regularly produced a decline in blood pressure, while sodium salt just as regularly produced a rise." Langford and Watson[199] drew attention to the report of Bartorelli et al.[205] that acute infusion of potassium is natriuretic and will reduce the blood pressure of hypertensive patients. The work of Sasaki et al.[200] offers the most convincing evidence of the long-term protective effect of potassium against excess sodium intake in man. However, debate continues as to whether sodium intake is "important" in human hypertension. As Page[22] remarks, "about once every generation salt is rediscovered. So it is referred to as common."

The animal models indicate that, for any given sodium and potassium intake, and depending upon the genetic mix, there will be some blood pressure that is characteristic of that intake. Blood pressure will be higher in a "sensitive" strain and lower in a "resistant" strain if the population is made up of some animals with each kind of genetic material and if there is enough sodium in the diet to bring out the hypertensive trait and not so much potassium it will be masked. This is the *saturation effect*. If all the members of a population are eating

a diet with sodium substantially in excess of requirement, everyone who is genetically predestined to have salt-induced hypertension will do so, where those lacking the salt-sensitive trait will remain normotensive and there will be no particularly characteristic distinction between the salt intake (or urinary sodium excretion) of normotensive and hypertensive subjects. The system is saturated.

Clinical Implications

Risk factors in hypertension: Epidemiologic studies have amply documented that certain measurable factors indicate increased susceptibility to hypertension. Some of these, although highly correlated with later development of hypertension, cannot be altered. It is generally true that no one factor, or any identified combination of factors, can specifically identify a person whose blood pressure is now "within normal limits" as one who is definitely destined to become hypertensive. The implications of the "tracking phenomenon," particularly applicable to those whose blood pressures are already at or even somewhat above the "upper limit of normal," has also been discussed. Evidence was presented that our accepted definition of "upper limit of normal" is probably wrong. Most young people whose pressure is "at the upper limit of normal" are actually hypertensive, but these identifiable candidates for serious elevation of arterial pressure later in life are only a fraction of those destined to become hypertensive. The others are "hidden" in the middle zone of the array of blood pressures near the mean for the age and sex in question. Part of this effect, as indicated earlier, is due to the upward displacement of the entire distribution of blood pressures in the American population. Factors that contribute most importantly are genetic susceptibility to hypertension, the "high sodium-low potassium environment" and psychosocial stress. Although obesity is clearly a correlate of hypertension, Dahl et al.[204] produced some quite convincing evidence that the higher salt intake of the heavy eater is the real determinant.

Importance of low sodium-high potassium diet: Some are not certain how important excess salt intake may be in the etiology of hypertension. However, there is no question that reduced sodium intake can be therapeutic in many patients with essential hypertension.[135–137] It is well established that hypertensive patients who respond to diuretic agents with an appreciable reduction of arterial pressure also respond to low sodium diets.[136,137] There is now an extensive body of evidence from both animal models[27,202] and human studies[200] that a large intake of potassium is protective against the hypertensigenic and probably other toxic effects of excess dietary sodium chloride. Most Americans consume daily an amount of sodium that is greatly in excess of nutritional requirements.[146] Custom in the preservation, marketing and preparation of foods greatly increases dietary sodium and concurrently depletes potassium.[150] It is therefore rational, in treating hypertension, first to institute a dietary regimen as low in sodium and as high in potassium as possible without going to such extremes as dialyzed milk and other expensive foods. This is *not* the current general recommendation of authoritative bodies sponsoring nationwide educational efforts to ameliorate the havoc of hypertension. Their recommendation is to embark immediately upon diuretic therapy "in those who require treatment" and to do no more about sodium intake than to counsel against "abuse" of salt. This may be a wise recommendation because long experience has shown that the "low sodium diet" alone has not proved effective in the clinic or office practice of medicine.[138] Nevertheless, it is rational to begin with such a moderate low sodium-high potassium regimen for two reasons. First, it will control blood pressure in an appreciable number of patients. Second, the effective dose of a diuretic agent, should it be needed, will be smaller.[137]

One would be naive to believe that dietary intervention would meet with success in all instances. Were this the case, low sodium diets would already have a larger place in the management of hypertension among ambulatory patients. There will be a spectrum of degree of compliance with such dietary recommendations. This compliance is measurable by sodium and potassium analysis of urine. In this regard, there will inevitably also be a spectrum of "success" in the urinary data. First, as noted above, there is a discordance between sodium and potassium content in the 24 hour urinary collection and the mean for 6 days of collection, with, for example, correlation coefficients of about 0.7 to 0.8 for 24 hour collections versus 6 days' collection in one carefully performed study.[199]

Management of a young person with borderline hypertension: An adult with high blood pressure has a life-shortening condition, and his outlook for the future is better if he is treated. We argue that more emphasis should be put upon the low sodium-high potassium diet as the primary maneuver but are aware that it is hard to achieve. However, the problem is different with young people who do not have definite elevations of pressure.

The only studies we know of medication in young people with borderline hypertension are the proposal of E. H. Kass to use a "small amount of diuretics" for "a short time" in children *with* essential hypertension to see whether that will "get them off the track" and Pierre Biron's trial of the beta adrenergic blocking agent propranalol in 10 children "with essential hypertension," 8 to 17 years of age. Biron gave a placebo for 4 months, then the drug for 4 months. There was "an average reduction of 25 mm Hg in the children's systolic pressure. The children all said they 'felt better' while receiving the drug and no side effects were noted." Biron is quoted as stating that ". . . there is a big question as to whether these children should be treated with such a drug for 10 to 20 years with eventual possible toxic effects . . ." [27] If the hypertension or the "susceptibility" to it is real, 10 to 20 years of treatment should be too short a time. In our view treatment of hypertension is a life-long problem. Elderly rats that eat too much salt become hypertensive.[128] We think dietary intervention would be more rational than drug treatment. It obviously will have to be on an individual basis because it

will be a long time before the high sodium-low potassium environment is changed.

Rational program for the hypertension-prone normotensive person: One might speculate that a rational clinical algorithm for the management of a normotensive patient thought to be hypertension-prone might look something like this:

1. By careful history taking, ascertain if there is hypertension in the parents, grandparents, uncles and aunts or among the siblings.
2. If the family has no hypertension and the blood pressure is in the mid-normal range, observe it at reasonable intervals. Unless it shows an upward trend, congratulate the patient.
3. If the family has hypertension or if the once normotensive patient shows an upward trend of the blood pressure, resolve to intervene.
4. Review your malpractice insurance and the laws and policies pertinent to informed consent.
5. Depending upon the conclusions reached in Step 4, decide whether to prescribe a diet reasonably low in sodium and high in potassium or whether to make a therapeutic trial of an antihypertensive drug. Reflect upon the consequences of giving a drug for high blood pressure to someone who does not have high blood pressure in the commonly accepted sense of the word. Reflect also upon the fact that a substantial reduction of blood pressure in the latter case might provide some pretty clear-cut evidence the patient *did* have high blood pressure. Remember that some drugs (if you give enough) will reduce anyone's blood pressure. Better study which drug to give.
6. Most patients with essential hypertension respond to saluretic diuretic agents. Evidence indicates that these are the same patients who respond to salt restriction with a diminution in extracellular fluid volume.[138] Not all patients with hypertension respond to saluretic diuretic drugs *or* a low salt diet in spite of a reduction in extracellular fluid.[4,133] If your patient has a strong family history of hypertension you may want to press further. Some patients do respond to the addition of propranolol.
7. Even if a drug should produce some pretty good evidence that your patient is really a candidate for serious hypertension, you would probably want to treat with diet rather than drug since your patient is now looking at a lifetime problem. Remember that it takes nearly 3 years to show that rats that eat a correct diet live longer than rats that eat too much salt and not enough potassium. It will not be in your lifetime or ours that the point will be proved in man, since a year for man is about 10 days for a rat. Have faith in the animal model. Comfort yourself with the thought that it would be hard to sue you for prescribing a rational diet. Continue to observe the blood pressure. If it continues an upward trend in spite of a reasonably low sodium-high potassium diet, there is time enough to initiate appropriate drug therapy.

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Addendum

Since submission of this manuscript, a new paper by Derek Denton has come to the attention of the authors: "Hypertension: A Malady of Civilization?" (In, Systemic Effects of Antihypertensive Agents (Sambhi MP, ed). Stratton Intercontinental Medical Books, New York, 1976, p 597–583), which gracefully develops the evolutionary thesis we have discussed above:

"Given the pivotal role of Na in the expression of the hypertensive process, a legitimate question follows. Can it be concluded that a high maternal salt intake, followed by a high intake during infancy and childhood, which then is sustained by induced hedonic preference through the next three to four decades of life is of little or no relevance to the basic genesis of hypertension in the Western urban community? . . .

"I would like to consider this question in a phylogenetic context on the basis that high salt intake is essentially a new nutritional situation of the past hundred years or so of civilization. This can be set against the fact that the physiological character of the appetite and regulatory metabolic systems of primates and man have evolved over millions of years under conditions where dietetic Na intake has been low and K+ intake high . . . perhaps the high salt intake from infancy to middle age of a large segment of the population in Western communities is an important factor in the causal expression of other jointly sufficient and severally necessary factors which, in the long term, contrive the hypertensive state."

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Role of Hypertension in Atherosclerosis and Cardiovascular Disease

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Clinical, experimental and pathologic studies strongly indicate that hypertension is a major factor in coronary heart disease, sudden death, stroke, congestive heart failure and renal insufficiency. The deleterious effect of the elevated blood pressure on the cardiovascular system appears to be due mainly to the mechanical stress placed on the heart and blood vessels. Humoral factors and vasoactive hormones such as angiotensin, catecholamines and prostaglandins may play a role in the pathogenesis of hypertensive cardiovascular disease but this role has not yet been defined and is probably secondary.

Hypertension, and the resulting increase in tangential tension on the myocardial and arterial walls, leads to the development of hypertensive heart disease and congestive heart failure as well as hypertensive vascular disease that affects not only the kidneys but also the heart and brain. Hypertensive vascular disease involves both large and small arteries as well as arterioles and is characterized by fibromuscular thickening of the intima and media with luminal narrowing of the small arteries and arterioles. The physical stress of hypertension on the arterial wall also results in the aggravation and acceleration of atherosclerosis, particularly of the coronary and cerebral vessels. Moreover, hypertension appears to increase the susceptibility of the small and large arteries to atherosclerosis. Thus the patient with hypertension is a candidate for both hypertensive and atherosclerotic vascular disease of the coronary and cerebral vessels leading to occlusive disease of both the large and small arteries and resulting in myocardial infarction and stroke. Other major complications of hypertensive vascular disease include rupture and thrombotic occlusion of blood vessels, especially in the brain.

Disease of the arterial media, which begins in childhood with the deposition of calcium in the vessels, may be an important cause of arterial hypertension. This form of hypertension may manifest itself in adults as arteriosclerotic hypertension and lead to cardiovascular complications very similar to those of essential hypertension. The relation of arteriosclerotic hypertension to nutritional factors, including dietary salt intake, deserves study.

Disease of the cardiovascular system is the leading cause of death in this country, and arteriosclerotic heart disease and stroke account for most of the mortality and morbidity.[1] There is substantial clinical and experimental evidence that hypertension is one of the most important etiologic factors in cardiovascular disease. More than 50 percent of patients with heart and blood vessel disease have hypertension and a greater percentage have underlying arteriosclerosis. Hypertension is estimated to be the cause of one fourth to one half of all cardiovascular deaths and it is present in epidemic proportions in this country. National health surveys indicate that about 15 percent of American adults have definite hypertension and another 15 percent have borderline hypertension.

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There is considerable evidence that control of blood pressure will prevent many of the cardiovascular complications of hypertension including congestive heart failure, hemorrhagic stroke, progressive renal damage, dissecting aneurysm and accelerated hypertension.[2–5] Although it has not been established that antihypertensive treatment reduces the atherosclerotic complications of hypertension, the clinical and experimental evidence strongly suggests that the early detection and treatment of hypertension could result in substantial reduction in morbidity and mortality from coronary atherosclerotic heart disease and atherothrombotic stroke. This paper reviews the pathologic and physiologic factors that may influence the course and treatment of hypertensive cardiovascular disease.

Interrelations Between Hypertensive and Atherosclerotic Vascular Disease

Hypertensive vascular disease and atherosclerotic vascular disease are separate disorders that cause similar but distinguishable biochemical and pathologic changes in the arteries. Both diseases lead to obstructive vascular lesions, but the patterns of distribution differ. Atherosclerosis mainly affects large and medium-sized vessels, whereas hypertensive vascular disease is primarily a disease of small arteries and arterioles although it also causes changes in large vessels. Atherosclerosis, when associated with hypertension or diabetes, also may involve small arteries, particularly those in the brain and heart. Studies on the natural history and epidemiology of atherosclerosis indicate that hypertension accelerates the progression of atherosclerosis in all populations.[6] As seen at autopsy, atherosclerosis of the aorta, coronary arteries, cerebral arteries and other major vessels is more extensive and more severe in hypertensive than in normotensive subjects. These studies also suggest that the effect of hypertension on the development of clinical coronary artery disease is influenced by the severity of preexisting atherosclerosis.

Although hypertension can aggravate atherosclerosis, it is not clear from experimental, pathologic and epidemiologic studies that hypertension itself, in the absence of other atherogenic factors, can cause atherosclerosis. However, it is well established that hypertension leads to the development of hypertensive vascular disease. Recent studies[7] in the cynomolgus monkey with hypertension produced by coarcting the thoracic aorta demonstrated that animals fed a low cholesterol diet did not manifest complicating atherosclerosis but had arterial changes characteristic of hypertensive vascular disease. The experimentally produced hypertensive lesions involved not only the larger arteries such as the coronary and cerebral vessels but also the small branches of these arteries. The changes in the large and small arteries appeared to be similar and included thickening of both the intima and media. The thickening of the cerebral vessels as well as the small extramural and intramural branches of the coronary arteries appeared to produce significant luminal narrowing (Fig. 1 and 2). The intimal lesions were usually focal, whereas the thickening of the musculoelastic media appeared to involve the entire vessel. These vascular changes occurred in the arteries proximal but not distal to the coarctation, thus suggesting that they are caused by high blood pressure with a resulting increase in tangential stress on the arterial wall.

Pathology of the intimal and medial lesions: The thickening of the intima and media in the hypertensive vessel appeared to be due to fibrocellular proliferation with deposition of acid mucopolysaccharides. Similar intimal and medial changes have been described in the coronary arteries of patients with coarctation of the aorta.[8] These findings are consistent with previous biochemical and metabolic studies indicating that thickening of the arterial media in hypertension is due to hyperplasia and hypertrophy of the medial smooth muscle cell as well as an increase in the content of collagen, elastin, acid mucopolysaccharides and electrolytes and water in the arterial media.[9–13]

In both hypertension and atherosclerosis the intimal lesions are focal and characterized by proliferation of cells, connective tissue and acid mucopolysaccharides. One major difference is the accumulation of lipid in atherosclerotic lesions and the absence of excess lipid in hypertensive lesions. These findings are consistent with earlier observations that hypertension has a major effect on the metabolism of the acid mucopolysaccharides and connective tissue proteins of the arteries without necessarily altering the metabolism of lipids or the influx of plasma cholesterol and lipoproteins into the arteries.[9,14,15]

Acceleration of atherosclerosis by hypertension: Studies in subhuman primates and other animal models support the findings in man that hypertension accelerates and aggravates atherosclerosis.[16–21] When monkeys with hypertension induced by coarctation of the thoracic aorta were fed a hypercholesterolemic diet, they had more severe atherosclerotic involvement of the vessels above the coarctation, particularly the coronary and cerebral arteries, than that of normotensive monkeys fed the same diet.[7] The hypertensive monkeys also manifested severe atherosclerosis of the small branches of the coronary and cerebral arteries, whereas these vessels (as well as the major cerebral arteries) were uninvolved in the normotensive monkeys. The distribution of the atherosclerotic lesions appeared to be the same as the distribution of the hypertensive vascular lesions found in monkeys with coarctation fed a low cholesterol diet. These findings suggest that the fibrocellular thickening of the intima of the large and small arteries caused by hypertension increases the susceptibility of these vessels to atherosclerosis. The findings also could explain the increased risk in hypertensive persons that premature clinical coronary and cerebral vascular disease will develop.

The actual mechanism by which hypertension aggravates atherosclerosis has not been established. However, the available evidence appears to indicate that the changes in connective tissue metabolism and endothelial permeability associated with atherosclerosis are increased by hypertension. In both hypertension and atherosclerosis an increase in vascular permeability as well as an augmented biosynthesis of deoxyribonu-

cleic acid (DNA), collagen, elastin and acid mucopolysaccharides in the arteries has been reported.[9–10,22–29]

Classification of Hypertensive Vascular Disease and its Complications

Vascular complications: The vascular complications of hypertension (Table I) may be classified into three broad categories or stages according to the pathology of the disease and its association with atherosclerosis. These categories include (1) hypertensive vascular disease, (2) hypertensive and atherosclerotic vascular disease, and (3) hypertensive and arteriosclerotic vascular disease, which consists of diseases related to atherosclerosis, calcific medial sclerosis and arteriolosclerosis. The stage of the vascular disease appears to be related to the age of the patient and the duration



FIGURE 1. Histologic appearance of a basilar artery from a monkey fed a low cholesterol diet after hypertension induced by coarctation of the thoracic aorta. The artery and its small branches show marked thickening of the musculoelastic media. The intima of the basilar artery is noticeably thickened by proliferative changes of the elastic and collagen fibers. Luminal narrowing appears to result from these changes. (Weigert-van Gieson ×200, reduced by 21 percent.)

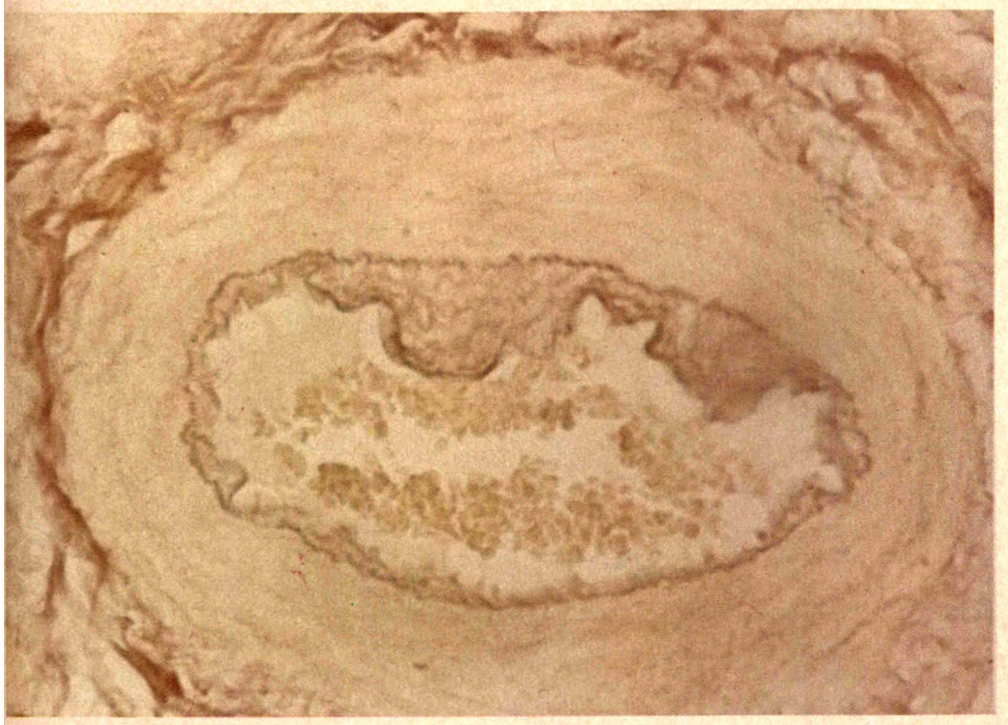


FIGURE 2. Histologic appearance of a small extramural branch of the left coronary artery of a monkey fed a low cholesterol diet after hypertension induced by coarctation of the thoracic aorta. The intima is irregularly thickened and shows proliferation of elastic and collagen fibers. No lipid is seen. The thickened intima and media appear to reduce the caliber of the vessel. (Weigert-van Gieson ×500, reduced by 27 percent.)

of the hypertension. Hypertensive vascular disease usually begins before the age of 35 years and progresses with age. After age 40, the disorder is frequently associated with atherosclerotic disease and after age 55 with diffuse arteriosclerosis.

In uncomplicated hypertensive vascular disease, as described earlier, both the large and small vessels show arterial sclerotic changes characterized by fibromuscular thickening of the intima and media with marked deposition of acid mucopolysaccharides. In accelerated or malignant hypertension, the proliferative changes in the arteries, particularly the small arteries and arterioles, are often followed by necrotic changes that may result in the formation of microthrombi, microinfarcts and rupture of vessels. Degenerative changes in the musculoelastic media also can occur in "benign" forms of hypertension and lead to the formation of saccular and dissecting aneurysms. Arteriolar hyalinization and elastic hyperplasia are recognized manifestations of benign hypertension although they also occur with increased frequency in the elderly and in patients with diabetes. On the other hand, necrotizing arteriolitis, fibrinoid degeneration and cellular hyperplasia or "onion skin lesions" are usually considered pathognomonic of malignant hypertension.

Hypertensive versus atherosclerotic complications: The sequelae of hypertension may also be classified clinically into hypertensive or atherosclerotic complications. Hypertensive complications are those directly due to hypertension. They appear to be caused by the direct mechanical effects of the hypertension on the heart and blood vessels and are preventable with effective antihypertensive treatment. These complications include (1) left ventricular hypertrophy, (2) congestive heart failure, (3) dissecting aneurysms, (4) hypertensive retinopathy, (5) malignant hypertension, (6) hypertensive crises or encephalopathy, (7) intracerebral and subarachnoid hemorrhage, and (8) renal failure. The atherosclerotic complications of hypertension are manifestations mainly of advanced atherosclerosis and include (1) coronary heart disease and its sequellae of angina pectoris, myocardial infarction and sudden death, (2) atherothrombotic strokes, (3) aortic aneurysm, (4) peripheral vascular disease, and (5) renal arterial stenosis. The atherosclerotic complications are much more difficult to control than the hypertensive complications and are largely responsible for the morbidity and mortality in both the treated and untreated hypertensive patient.

Pathogenesis of Hypertensive Vascular Disease

The major mechanisms that have been implicated in the pathogenesis of hypertensive vascular disease are schematically outlined in Figure 3. Many of these mechanisms are similar to those described previously[15] in the production of atherosclerotic vascular disease. According to current concepts, two types of cells in the arterial wall play key roles in the development of hypertensive vascular disease (as well as atherosclerotic vascular disease). These are the arterial smooth muscle cell responsible for the metabolic changes in the artery, and the endothelial cell, responsible for changes in permeability. The endothelial cell lining the arterial intima has been shown to contain contractile proteins[30] that probably participate in the regulation of vascular permeability by altering the openings between the interendothelial junctions.

Increased vascular permeability—the endothelial cell: The transport of material across the endothelium can take place by intercellular and transcellular routes. The available evidence suggests that under normal conditions passage through intercellular clefts is restricted to small and medium size particles with a diameter of less than 90 Å, whereas macromolecules, including proteins and lipoproteins, are carried through the cell solely by pinocytosis.[31–33] Under abnormal conditions in which the endothelial cells are damaged or are exposed to relatively high concentrations of vasoactive amines such as angiotensin, histamine, serotonin and catecholamines, contraction of endothelial cells may occur and thereby permit the passage of macromolecules as well as small molecules through the interendothelial junctions.[34–37]

There is considerable morphologic and physiologic evidence that intimal permeability of the arteries is increased in experimental hypertension, particularly

TABLE I

Classification of Hypertensive Vascular Disease and Complications

I. Hypertensive vascular disease
  A. Large and medium-sized vessel disease
    1. Arterial sclerosis
      a. Fibromuscular thickening of arterial wall (might predispose to atherosclerosis and thrombosis)
    2. "Berry" aneurysm
      a. Rupture with subarachnoid hemorrhage
      b. Tumor syndrome
    3. Dissecting aneurysm
      a. Rupture and hemorrhage
      b. Arterial occlusion
  B. Small vessel disease
    1. Arterial sclerosis of small arteries
      a. Fibromuscular thickening of arterial wall (might predispose to atherosclerosis and thrombosis)
      b. Luminal narrowing and resulting ischemia
      c. Luminal narrowing with thrombosis and microinfarcts
    2. Arteriolar sclerosis
      a. Benign lesion
        1. Luminal narrowing with ischemic changes
      b. Malignant lesion (arteriolonecrosis)
        1. Luminal narrowing with ischemia
        2. Luminal narrowing with microthrombi and microinfarcts
        3. Rupture with focal hemorrhage
        4. Microangiopathic hemolytic anemia
II. Hypertensive and atherosclerotic vascular disease
  A. Hypertensive vascular disease (as above) (*plus*)
  B. Atherosclerotic vascular disease of both large and small arteries
    1. Luminal narrowing with ischemia, ischemic necrosis and fibrosis
    2. Atherothrombotic occlusion with infarction
    3. Emboli from mural thrombus of plaque
    4. Cholesterol emboli from ulcerated plaque
III. Hypertensive and arteriosclerotic vascular disease
  A. Hypertensive vascular disease (as above) (*plus*)
  B. Atherosclerotic vascular disease (as above) (*plus*)
  C. Calcific medial sclerosis
    1. Arteriosclerotic hypertension
    2. Arteriosclerotic aneurysm
    3. Dissecting aneurysm

when the disease is severe or in its early stages. Duncan et al.[25] have demonstrated in the dog with experimentally induced hypertension that elevation of blood pressure greatly accelerates the passage of labeled albumin from the plasma into the inner layers of the proximal portion of the aorta. These workers[38] as well as Fry[39] have shown that increased tangential stress or stretching of the aortic wall, rather than increased pressure as such, increases the flux of serum albumin across the endothelial surface of the thoracic aorta in vitro. Carew and Patel[40] have presented evidence that the influx of dye-tagged albumin into the isolated perfused left coronary arteries of the dog also increases with increases in arterial pressure and tangential stress as well as with increases in shear stress.

The increase in vascular permeability reported in different forms of experimental hypertension appears to be due to an increase in transendothelial transport and to an opening and widening of the interendothelial junctions. Actual pathologic damage to the endothelial cells also may occur during severe hypertension and result in hyperpermeability.

Giese,[41] Jellinek[42] and others have advanced the concept that an increase in vascular permeability with resulting insudation of plasma and plasma proteins into the arterial wall is primarily responsible for the development of hypertensive vascular disease. Vascular hyperpermeability also has been demonstrated in atherosclerosis and likewise is believed by many workers to play a key role in the development of this disease. It has been postulated that injury to the endothelial cell by an atherogenic stimulus, such as hyperlipidemia, increases vascular permeability to plasma low density lipoproteins that act on the arterial smooth muscle cell to initiate the atherosclerotic process. Although increased amounts of lipids and low density lipoproteins have been demonstrated in atherosclerotic vessels, they have not been shown to be present in uncomplicated hypertensive lesions.[43]

Hypertrophy and hyperplasia of arterial smooth muscle cell: The arterial smooth muscle cell is the predominant cell in the artery and is present in increased numbers in the thickened intima and media of the hypertensive artery. Large number of these cells are also present in the raised intima of atherosclerotic vessels. The smooth muscle cell is a multifunctional cell[44–46] that in the presence of hypertension (or an atherogenic stimulus) multiplies and synthesizes increased amounts of acid mucopolysaccharides, collagen and elastin.[28,47–49] An increased synthesis of DNA, ribonucleic acid (RNA) and protein also occurs in hypertensive vessels[10,50,51] and probably reflects proliferation of the smooth muscle cell. Hypertrophy of the smooth muscle cell is also a characteristic finding and is manifested chemically by an increase in the RNA to DNA ratio in the hypertensive artery. There is growing evidence that the endothelial cell, like the medial smooth muscle cell, is a multifunctional cell that can synthesize fibrous proteins and change into an intimal smooth muscle cell.[44,52]

As shown in Figure 3, hypertension and the resulting increase in tangential tension or stretch on the arterial wall may affect the smooth muscle cell and endothelial cell directly; or, the effects may be indirect, mediated through plasma and tissue factors such as platelets, plasma proteins and vasoactive hormones including angiotensin, histamine, catecholamines and the prostaglandins. The arteries appear to respond in a uniform manner to an increase in blood pressure regardless of the cause or level of plasma renin activity (Tables II and III). The characteristic changes include thickening of the vessel wall, increases in the weight and water con-

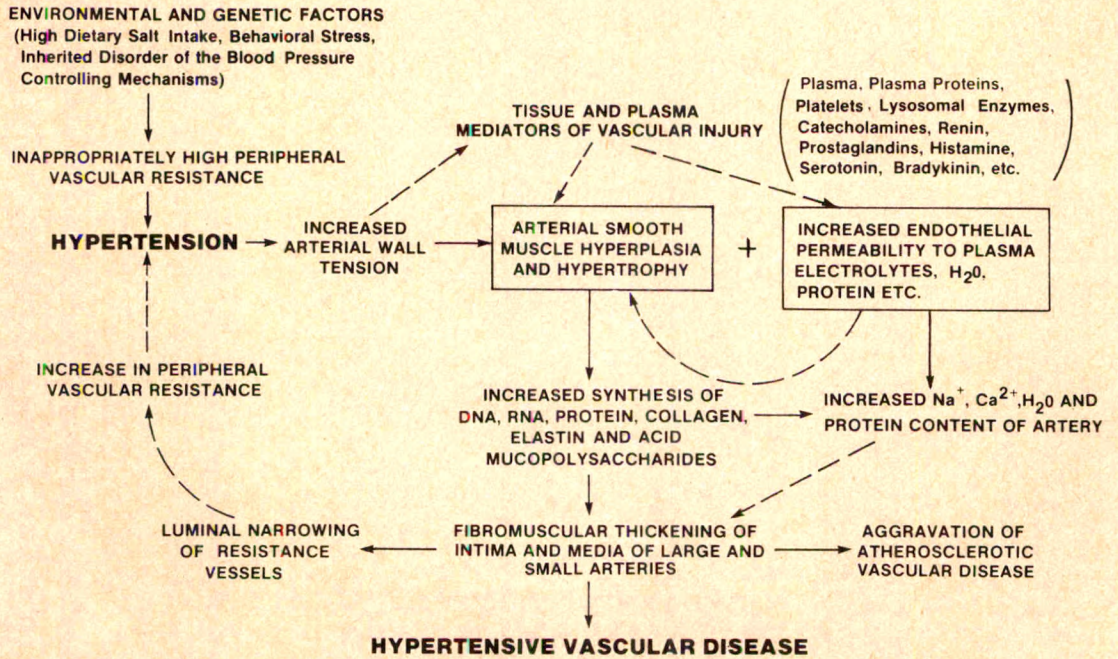


FIGURE 3. Unified concept of hypertensive vascular disease.

tent of the artery and significant increases in the absolute amount of protein, collagen, elastin, DNA and RNA contained in the artery. The most pronounced changes are in the protein and RNA content of the vessel. These findings, together with an increase in the RNA to DNA ratio, are consistent with significant hypertrophy as well as hyperplasia of the arterial smooth muscle cell.

Vasoactive Hormones and Vascular Disease

Renin and angiotensin: That renin may induce or accelerate vascular disease is an attractive concept[53] and is consistent with the experimental data[54–56] showing that exogenous angiotensin is capable of increasing vascular permeability and causing damage to the arteries. This concept, although not established, is an important one deserving further study. At present there is no good evidence in clinical or experimental hypertension that plasma renin plays a primary role in the pathogenesis of vascular disease. The available data indicate that the vascular complications of hypertension are primarily related to the duration and severity of the hypertension and its mechanical effects on the arterial wall. However, a secondary role of renin and angiotensin in vascular disease is not excluded because renin activity of the plasma frequently increases in severe hypertension as a result of vascular damage to the kidney produced by the high level of blood pressure. Renin and angiotensin contained in the arterial wall may also play a role in vascular injury. Renin-like activity[57,58] and angiotensin I-converting enzyme activity[59] have been demonstrated in the arteries, and recent immunohistochemical and tissue culture studies indicate that these enzymes are contained in the endothelial cells.[60,61] Earlier studies[56] have indicated a role for the arteries in inactivating angiotensin.

Other vasoactive hormones in arterial wall: The arterial wall contains in addition to renin other vasoactive hormones that also could influence its function by altering vascular permeability, metabolism and contractility.[56,62] These hormones appear to be synthesized and released by the arteries and include norepinephrine, histamine and the prostaglandins.[56,63–65] Recently a vasodepressor factor with potent vasodilating properties has been identified in the vessels.[66,67] Both the endothelial cell and arterial smooth muscle cell grown in tissue culture have been shown to synthesize PGE_2 and $PGF_{2\alpha}$[68–70] with synthesis apparently being enhanced by angiotensin and bradykinin.[65,68,69] There is also some evidence that the synthesis and metabolism of the prostaglandins may be altered in certain forms of experimental hypertension.[70,71] Investigation of histidine decarboxylase activity of the arteries suggests that the synthesis of histamine by the endothelial cells of the aorta is increased in experimental hypertension and atherosclerosis.[72]

Histamine and serotonin: In addition to the arterial smooth muscle cell and endothelial cell, the periarterial mast cell appears to synthesize several different vasoactive hormones such as histamine and serotonin.[73] The mast cell also appears to be capable of storing and releasing large amounts of these hormones. There is growing evidence that this cell accumulates in large numbers in the adventitia of vessels containing fibrous

TABLE II

Blood Pressure and Plasma Renin in Mineralocorticoid- and Renal-Induced Hypertension in the Rat* (mean ± standard error)

	Mineralocorticoid Study		Renal Study	
	Control	DOC Hypertension†	Control	Renal Hypertension†
Body weight (g)	342 ± 7	352 ± 6	365 ± 5	350 ± 8
Blood pressure (mm Hg)	108 ± 6	187 ± 8§	104 ± 5	185 ± 9§
Plasma renin (ng/ml per hour)	3.4 ± 0.3	0.9 ± 0.1§	3.8 ± 0.4	12.4 ± 1.4§

* See Reference 123.
† Hypertension was induced by weekly subcutaneous injections of 10 mg deoxycorticosterone (DOC, Percortin) for 6 weeks with 1 percent sodium chloride in drinking water.
‡ Two-kidney renal hypertension was produced by clipping the left renal artery for 8 weeks.
§ Probability (*P* value) <0.01.

TABLE III

Chemical Composition of Aorta of Rats with Mineralocorticoid- and Renal-Induced Hypertension (mg/aorta)* (mean ± standard error)

	Mineralocorticoid Study			Renal Study		
	Control	DOC Hypertension†	% Δ	Control	Renal Hypertension†	% Δ
Aortic wet weight	40.22 ± 0.82	58.14 ± 1.21	+44.6	50.11 ± 1.20	71.03 ± 1.43	+41.7
Aortic water content	28.81 ± 0.70	41.73 ± 0.94	+44.8	36.42 ± 0.91	51.85 ± 1.33	+42.4
Aortic dry weight	11.40 ± 0.25	16.40 ± 0.19	+43.9	13.75 ± 0.28	19.27 ± 0.17	+40.1
Protein	2.40 ± 0.05	4.12 ± 0.08	+71.7	3.42 ± 0.07	5.81 ± 0.09	+69.9
Elastin	5.10 ± 0.10	7.09 ± 0.13	+39.0	6.61 ± 0.13	8.92 ± 0.12	+34.9
Collagen	1.48 ± 0.04	2.01 ± 0.05	+35.8	2.26 ± 0.07	3.16 ± 0.06	+39.8
Cholesterol X 10	0.52 ± 0.02	0.79 ± 0.02	+51.9	0.66 ± 0.03	0.99 ± 0.04	+50.0
DNA X 10	0.73 ± 0.02	1.01 ± 0.02	+38.4	0.92 ± 0.02	1.25 ± 0.03	+35.9
RNA X 10	0.95 ± 0.02	1.59 ± 0.03	+67.4	1.02 ± 0.02	1.70 ± 0.03	+66.6

* See Reference 123.
† Hypertension induced as shown in Table II.

plaques,[74] and recent evidence[7] suggests that there is an increased number of these cells in hypertensive vessels.

Platelets and Vascular Disease

Platelets and vasoactive substances: The role of platelets in hypertensive vascular disease is not clear although platelet aggregates have been described on the endothelial surface of hypertensive vessels.[75] Evidence has been presented that many factors leading to vascular injury may cause platelet aggregation and the release of platelet constituents, many of which are vasoactive and potentially inflammatory and atherogenic.[76] The vasoactive substances that are releasable by platelets include adenosine diphosphate, histamine, serotonin, epinephrine and prostaglandins (PGE_2, $PGF_{2\alpha}$). Recent reports also suggest that aggregating platelets may release cyclic endoperoxides (PGG_2, PGH_2) and thromboxane A_2, which have potent vasoconstrictor activities.[77] In addition, the platelets appear capable of releasing elastase and other lysosomal enzymes that could act to damage the arterial wall. The platelets also have been shown to secrete a protein (platelet factor 4) that can neutralize heparin.[78] The activity of this factor as well as platelet factor 3, a membrane lipoprotein that accelerates coagulation, is reported to be elevated in atherosclerotic vascular disease.[79]

Arterial thrombosis: There is substantial evidence that platelets play a primary role in the thrombotic complications of atherosclerosis. There also is some experimental and clinical evidence that hypertension may precipitate arterial thrombosis by injuring the arterial intima or by rupturing the surface of an atherosclerotic plaque.[80] The interaction of blood platelets with exposed collagen or basement membrane of the artery to form platelet aggregates appears to be a fundamental mechanism involved in the initiation of thrombosis.[81,82] This mechanism probably accounts for the occurrence of occlusive thrombi at sites of rupture or ulceration of the surface of atherosclerotic plaques. Some of the vasoactive hormones produced and released by the arterial wall, such as PGE_2 and $PGF_{2\alpha}$, are also capable of causing platelet aggregation and conceivably could play a role in arterial thrombosis.

Abnormal platelet function: Abnormal platelet function has been reported in subjects who have had complications of atherosclerosis or in those who appear to be susceptible to the disease.[76] These abnormalities include shortened platelet survival time, increased platelet turnover and an increased platelet adhesiveness and aggregation. Although there may be a possible link between platelet reactivity and conditions such as hypertension that predispose to the development of atherosclerosis, this relation has not been established and requires further study.

Lysosomes and Vascular Disease

In recent years there has been a growing interest in the role of lysosomes in the pathogenesis of hypertensive and atherosclerotic vascular disease. Lysosomes are a heterogeneous group of cytoplasmic granules that contain acid hydrolases with widely different specificities. These enzymes appear to mediate the digestive and lytic processes of the cell and include the cathepsins, proteases, β-glucuronidase, β-N-acetylglucosaminidase, acid phosphophatase and DNA.

Damage to the endothelial cells and smooth muscle cells of the arteries may occur during both hypertension and atherosclerosis, and the release of lysosomal enzymes from these cells might interfere with the function of neighboring cells and thereby aggravate the disease processes. The inability of the degradative enzymes to keep pace with the biosynthetic processes of the cell may result in the intracellular accumulation of substances that also may impair cell function. A deficiency of the lysosomal enzyme cholesterol esterase in the smooth muscle cells of atherosclerotic vessels has been reported[83] and could explain the accumulation of cholesterol ester in the foam cells found in atherosclerosis. This enzyme deficiency does not appear to occur in hypertension. Lysosomal hydrolase activity has been found to be elevated in hypertensive and atherosclerotic vessels.[84–87] These changes of lysosomal activity may reflect increases in the turnover of the smooth muscle cells as well as increases in the biosynthetic activity of these cells.

An augmented synthesis of acid mucopolysaccharides[9,24] and an increased activity of β-glucuronidase and β-N-acetylglucosaminidase[84–87] have been demonstrated in hypertensive and atherosclerotic vessels. These changes of enzyme activity suggest an increased degradation of acid mucopolysaccharides, which may be reduced relative to the synthesis of these macromolecules since they are present in increased amounts in hypertensive and atherosclerotic vessels.[9,24] Recent studies in subhuman primates with hypertension and atherosclerosis[7,88] indicate that the acid mucopolysaccharides contained in the involved arteries may accumulate intracellularly as well as extracellularly.

Arterial Lipids and Vascular Disease

Lipid content in hypertensive versus atherosclerotic lesions: Hypertensive and atherosclerotic lesions are distinguished by their lipid content and composition. Atherosclerotic vessels contain increased amounts of lipids per gram of arterial tissue whereas the lipid concentration of hypertensive vessels is normal.[9,14,89] The excess lipid contained in the atherosclerotic lesions is histochemically demonstrable by staining with oil-Red-O or sudan black, whereas stainable lipids are not detectable in hypertensive vessels. The lipid accumulating in the greatest amount in atherosclerotic lesions at all stages of their evolution is cholesterol, especially ester cholesterol. In contrast, the concentration of free and ester cholesterol in hypertensive vessels is not increased. These observations are consistent with previous data[14,24] indicating a normal influx of plasma cholesterol into hypertensive vessels and an increased cholesterol flux into atherosclerotic vessels. The findings also are consistent with the biosynthesis of cholesterol ester in the arteries, which is reported to be normal in hypertensive vessels and increased in atherosclerotic vessels.[90,91]

Elevation of free cholesterol in hypertensive arteries: Although the concentration of cholesterol in the arteries is unaltered in hypertension, the absolute amount of cholesterol may be somewhat elevated as indicated by the total amount of cholesterol in the entire vessel or in an anatomically defined segment of the vessel. The increase in cholesterol appears to be due solely to an increase in nonesterified cholesterol. Ester cholesterol, which is present in much smaller amounts than free cholesterol in normal and hypertensive vessels, does not change in hypertension. The elevation of free cholesterol in hypertensive arteries is associated with an increase in DNA and RNA content (Table III) and is probably due to an increase in cell membrane cholesterol resulting from hypertrophy and hyperplasia of smooth muscle cells. Phospholipids, which are also major lipid components of cell membranes, show increases similar to those of free cholesterol. Cell proliferation with increased incorporation of cholesterol into the newly formed cell membranes also might account for the reported increased biosynthesis of cholesterol in hypertensive vessels. [92]

Hypertension, Coronary Heart Disease and Sudden Death

Hypertension is by and large the most important risk factor for coronary heart disease, although the fundamental disturbance in coronary disease is atherosclerosis. The results of several epidemiologic studies[93] indicate that the risk of every manifestation of coronary atherosclerotic heart disease, including angina, coronary insufficiency, myocardial infarction and sudden death, is significantly related to the antecedent level of both systolic and diastolic blood pressure.

Effects of hypertension on coronary arteries and myocardium: Numerous lines of evidence in animal models and man indicate that the adverse effects of hypertension on the course of coronary heart disease are due to the mechanical effects of a high level of blood pressure on both the coronary arteries and the heart muscle.[15] These effects are schematically presented in Figures 4 and 5. The physical (tangential) stress that hypertension places on the coronary arterial wall appears to cause (1) hypertensive vascular disease of the large and small coronary arteries, with the latter showing luminal narrowing in addition to fibromuscular thickening of the vessel wall, and (2) acceleration and aggravation of atherosclerotic vascular disease with extension of the disease to involve the small branches of the coronary arteries. The specific effects of hypertension on the coronary vessels and myocardium of man have not been elucidated. However, studies in subhuman primates[7] indicate that the hypertensive changes in the coronary arteries, especially in the presence of myocardial hypertrophy, may operate to cause myocardial ischemia. The hypertensive vascular changes likewise can act synergistically with the atherosclerotic changes in the vessels to cause marked reduction of coronary blood flow. There is also some evidence that hypertension may play a role in precipitating coronary thrombosis, although it is well established that atherosclerosis of the coronary vessels generally sets the stage for thrombosis and resulting myocardial infarction. The effect of hypertension and other risk factors on myocardial infarction has been reported to be potentiated by the oral contraceptive agents, which by themselves increase susceptibility to coronary thrombosis.[94] Diabetes, which appears to cause small coronary vessel disease and to accelerate coronary atherosclerosis, also enhances the effect of hypertension on ischemic heart disease.[6,95]

Hypertension and sudden cardiac death: The risk profile of sudden cardiac death is indistinguishable from

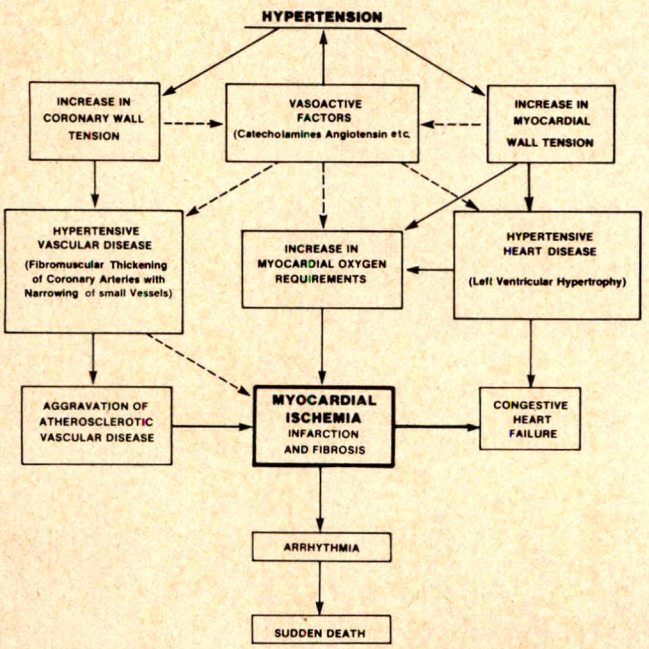


FIGURE 4. Role of hypertension in coronary heart disease.

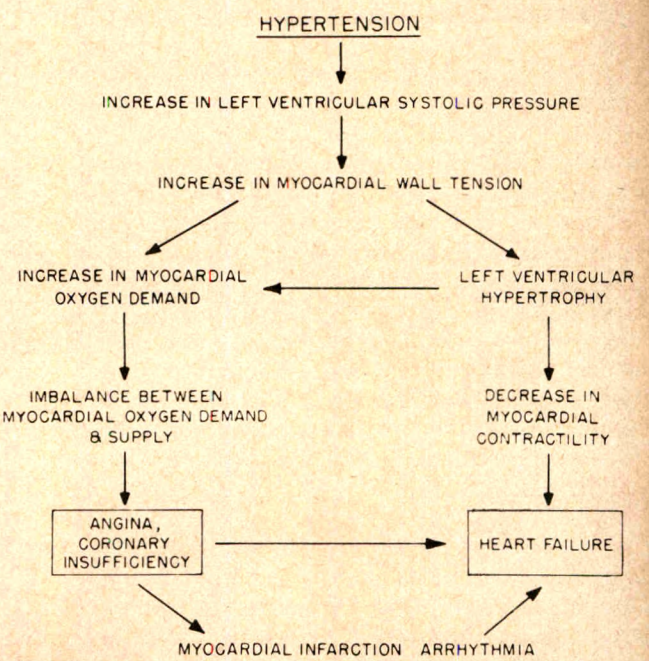


FIGURE 5. Adverse effects of hypertension on myocardial function.

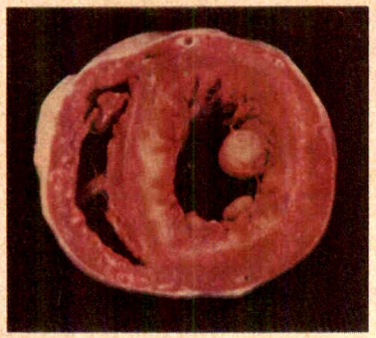


FIGURE 6. Heart slice from a hypertensive cynomolgus monkey that died suddenly and unexpectedly 6 months after coarctation of the thoracic aorta. The heart slice was prepared after perfusion of the heart with triphenyl tetrazolium chloride solution.[98] The zones stained red are intact myocardium. The pale unstained areas represent enzyme (dehydrogenase)-deficient ischemic myocardium involving the papillary muscle and posterior and septal walls of the left ventricle. The heart showed left ventricular hypertrophy without atherosclerotic narrowing of the coronary arteries. The small extramural and intramural branches show marked hypertensive vascular disease with fibromuscular thickening and luminal narrowing.

that of coronary heart disease with hypertension and an electrocardiographic pattern of left ventricular hypertrophy strongly correlated with increased risk of sudden and unexpected death.[96] Sudden coronary death has been shown to be associated with obstructive (atherosclerotic) coronary disease, usually involving several vessels.[97,98] Acute coronary thrombosis is relatively infrequent, occurring in about 25 percent of the cases. In about two thirds of sudden cardiac deaths there is either acute or old myocardial infarction; subendocardial lesions outnumber transmural lesions in acute infarction. In a minority cases of sudden cardiac death the coronary arteries have been reported to show less than 50 percent luminal narrowing. Some of the pathologic findings described in the heart of these patients include subendocardial necrosis, small coronary vessel disease and platelet aggregates in the coronary microcirculation.

Acute myocardial ischemia has been demonstrated histochemically in the majority of patients after sudden death.[97] These pathologic observations support the concept that sudden cardiac death results from myocardial ischemia produced by advanced coronary atherosclerosis. In the vast majority of cases the lethal event is ventricular fibrillation. There is growing evidence in animal models and in man with coronary heart disease that enhanced sympathetic nervous activity and psychologic stress may be important factors in precipitating ventricular fibrillation in the ischemic myocardium.[99] Consistent with these observations are recent data[100] suggesting that the incidence of sudden cardiac death in patients who have recovered from acute myocardial infarction is greatly reduced by beta adrenergic blocking drugs.

Sudden cardiac death has been observed in subhuman primates with experimentally induced hypertension and atherosclerosis.[7] The pathologic findings in the heart appear very similar to those described in human subjects who die suddenly. These findings include (1) severe atherosclerotic narrowing of two or more major coronary arteries as well as luminal narrowing of the large and small coronary branches; (2) focal myocardial ischemia and necrosis; and (3) marked hypertrophy of the left ventricle. Studies in the subhuman primate also indicate that hypertensive disease of the small coronary vessels without complicating coronary atherosclerosis but with myocardial hypertrophy is an important cause of sudden coronary death (Fig. 6). It is noteworthy that 45 to 68 percent of persons who die suddenly also show myocardial hypertrophy at autopsy.[98] It is possible that many of these patients had hypertension that, together with the myocardial hypertrophy, might have provided a background for generating myocardial ischemia and sudden death.

Hypertension and coronary insufficiency: The manner in which hypertension and myocardial hypertrophy may lead to coronary insufficiency is shown in Figure 5. The arterial pressure is an important hemodynamic determinant of coronary blood flow and myocardial oxygen consumption. Consequently changes in blood pressure can alter the balance between myocardial oxygen supply and demand—an imbalance that can result in myocardial ischemia. It is generally agreed that the major hemodynamic variables directly related to myocardial oxygen requirements include (1) the intramyocardial tension (product of ventricular systolic pressure and radius of the ventricle divided by its wall thickness), (2) the heart rate, and (3) the contractile state of the ventricle.[101] Variations of ventricular radius are related primarily to the end-diastolic volume, which is influenced by ventricular compliance, venous return and duration of diastole. In hypertension the left ventricular systolic pressure increases, resulting in an increase in the left ventricular intramyocardial tension. These changes and resulting left ventricular hypertrophy operate to increase myocardial oxygen requirements and thereby enhance the likelihood of angina pectoris and coronary insufficiency in hypertensive patients who have coronary disease with a relatively fixed coronary blood flow.[102,103] Elevation of heart rate is characteristic of hypertension and also may augment oxygen demand and risk of coronary insufficiency.

Effects of antihypertensive drugs: That hypertension itself increases susceptibility to myocardial ischemia is suggested by autopsy studies that indicate that angina pectoris may occur in hypertensive patients with only mild to moderate degrees of coronary atherosclerosis whereas in normotensive persons, the angina is almost always associated with severe coronary atherosclerosis involving multiple vessels.[104] The blood pressure reducing effects of the antihypertensive drugs operate to reduce the oxygen requirements of the heart muscle and thus may improve adequacy of the coronary circulation and reduce the frequency of anginal attacks.[105,106] Propranolol is especially useful in the treatment of angina since the drug reduces myocardial oxygen demand not only by lowering the blood pressure but also by slowing the heart rate and decreasing myocardial contractility.[107] Reserpine has similar effects on

the heart and also may be useful in the management of angina pectoris.[106] Certain antihypertensive vasodilating drugs such as hydralazine, minoxidil and diazoxide reflexively stimulate the sympathetic nervous system to increase heart rate and cardiac output. These effects may increase myocardial oxygen demand and thereby precipitate angina pectoris and coronary insufficiency in patients with coronary artery disease.[102,105] Combined use of the vasodilators with drugs like propranolol, reserpine and guanethidine that diminish sympathetic nervous activity may prevent or reduce the myocardial stimulatory effects of the vasodilating drugs and enhance their antihypertensive effectiveness.

Mechanisms of left ventricular hypertrophy in hypertension: Experimental studies of myocardial hypertrophy indicate that an increase in myocardial wall tension and resulting elevation of myocardial oxygen consumption initiate a series of biochemical events that result in left ventricular hypertrophy. These events include increases in protein and RNA synthesis by the myocardial cell and increases in DNA and collagen biosynthesis by the interstitial cells of the myocardium.[108–115] Increases in left ventricular weight and myocardial content of RNA and protein have been found as early as 48 hours after systolic overloading of the heart. At 11 days myocardial collagen content is also elevated. Although the increase in fibrous tissue in the hypertrophied heart may represent an adaptive response to an increase in myocardial wall tension, it also may be a consequence of a decrease of oxygen tension in the tissue fluids resulting from an increase in oxygen consumption by the hypertrophied heart. Studies on the control of collagen biosynthesis indicate that decreased oxygen tension in tissue fluids is a stimulus to the production of collagen by the fibroblasts.[116] Another important cause for myocardial fibrosis in hypertensive heart disease is myocardial ischemia caused by hypertensive disease of the coronary vessels. In addition to augmenting myocardial oxygen requirements, cardiac hypertrophy leads to a depression of myocardial contractility and cardiac performance and finally to congestive heart failure.[117–120]

In some patients with labile and borderline hypertension or with systolic hypertension, myocardial hypertrophy may also be related to an increase in cardiac output or an enhanced activity of the cardiac beta adrenergic receptors. There is good evidence that a chronic volume overload on the heart, which occur in high cardiac output states associated with anemia, arteriovenous fistula and hyperthyroidism, is a cause for myocardial hypertrophy. Vasodilator drugs such as hydralazine and minoxidil, which increase cardiac output, may also operate to cause myocardial hypertrophy[121] whereas drugs such as reserpine, propranolol and the diuretic agents, which prevent increases in cardiac output, may protect against myocardial hypertrophy.[122]

Sustained hypertension, regardless of its cause, appears to lead to characteristic chemical changes in the heart that result in left ventricular hypertrophy and hypertensive heart disease[123] (Table IV). These changes include increases in the myocardial content of protein, RNA, DNA and collagen in association with increases in heart weight. The changes in RNA are more pronounced than those of DNA and result in an increase in the ratio of RNA to DNA. Morphologic and radioautographic studies with labeled uridine and thymidine indicate that the increases in the DNA content of the heart are due to the proliferation of interstitial cells and not myocardial cells whereas the proportionately greater increases in RNA reflects the hypertrophy of the myocardial cell.[10,113,114] The degree of myocardial hypertrophy appears to be related mainly to the severity and duration of the hypertension[120,123] although there is some evidence that hormonal factors, such as the growth hormone and catecholamines, may influence the development of cardiac hypertrophy under certain experimental conditions.[124,125] A role for the renin-angiotensin system in myocardial hypertrophy has also been proposed.[121] In the experimental studies summarized in Tables II and IV, the effect of hypertension on the heart did not appear to be influenced by the level of plasma renin activity since the degree of myocardial hypertrophy, as indicated by heart weight and chemical composition, was comparable in low renin hypertension induced by injections of deoxycorticosterone (DOC) and in high renin (two-kidney Goldblatt) hypertension. Similar changes in the heart have been observed in genetic hypertension with normal plasma renin levels.[123]

TABLE IV

Chemical Composition of Heart of Rats With Mineralocorticoid- and Renal-Induced Hypertension (mg/heart)*

	Mineralocorticoid Study			Renal Study		
	Control	DOC Hypertension†	% Δ	Control	Renal Hypertension†	% Δ
Heart wet weight	990 ± 13	1280 ± 22	+29.3	1052 ± 16	1336 ± 24	+27.0
Heart water content	818 ± 14	1052 ± 15	+28.6	830 ± 12	1042 ± 13	+25.5
Heart dry weight	172 ± 5	228 ± 9	+32.6	222 ± 7	294 ± 10	+32.4
Protein	92 ± 1.5	130 ± 2.7	+41.3	104 ± 1.3	146 ± 3.0	+40.4
Collagen	8.50 ± 0.19	11.48 ± 0.34	+35.0	6.91 ± 0.15	9.23 ± 0.27	+33.6
DNA	1.61 ± 0.02	2.07 ± 0.02	+28.6	1.11 ± 0.02	1.42 ± 0.02	+27.9
RNA	2.42 ± 0.03	3.54 ± 0.04	+46.3	1.90 ± 0.02	2.82 ± 0.02	+48.4

* See Reference 123.
† Hypertension induced as shown in Table II.

Hypertension, Cerebral Vascular Disease and Stroke

Stroke is a clinical syndrome that results from cerebral ischemia or infarction. It is caused by obstruction or rupture of a cerebral artery. Obstruction is generally associated with atherosclerosis, whereas rupture is associated with sustained hypertension with or without severe atherosclerosis. Population surveys in the United States suggest that an atherothrombotic stroke is the most prevalent type of stroke, accounting for some 60 percent of cases.[126] Hemorrhagic stroke, due either to intracerebral or to subarachnoid hemorrhage, is reported to account for only 20 to 25 percent of strokes and embolic stroke may be responsible for about 10 to 15 percent. It appears from carefully performed autopsy studies[127] that intracerebral hemorrhage caused by rupture of an intracerebral microaneurysm is being underestimated as a cause of stroke.

Hypertension, diabetes and hyperlipidemia are important precursors of cerebral atherosclerosis, infarction and stroke. Of these, hypertension is clearly the most important etiologic factor of stroke.[126] Elevation of systolic blood pressure appears to have an effect in precipitating stroke at least comparable to that of diastolic blood pressure. The adverse effect of hypertension on the cerebral arteries appears to be due to the physical stress placed on these vessels by a high level of arterial pressure. These hypertensive effects, as schematically outlined in Figure 7, result in the development of hypertensive vascular disease and acceleration of atherosclerotic disease of the cerebral arteries.

Hypertension versus atherosclerosis: Experimental studies in subhuman primates indicate that both hypertension and hypercholesterolemia are major causes of cerebral atherosclerosis.[7] These factors appear to operate synergistically to produce cerebrovascular disease since hypertension and hypercholesterolemia, when studied alone, did not cause atherosclerosis. Hypertension alone also did not produce atherosclerosis in any of the other vascular beds, but the hypercholesterolemia induced by a high cholesterol diet did result in moderate to severe atherosclerosis of the aorta and mild atherosclerosis of the coronary arteries. These latter findings seem to reflect differences in the susceptibility of different vascular beds to atherosclerosis. They are consistent with the observations in man showing that atherosclerotic lesions appear first in the aorta, later in the coronary arteries and lastly in the cerebral arteries.[128]

Although studies in subhuman primates indicate that hypertension itself does not cause cerebral atherosclerosis, they clearly show that elevation of blood pressure produces hypertensive vascular disease of the brain that affects large arteries, small arteries and arterioles. The fibromuscular thickening of the cerebral arteries with luminal narrowing of the small arteries and arterioles appears to provide the background for cerebral ischemia and its complications. Experimental and clinical studies suggest that hypertension, even in the absence of atherosclerosis, may precipitate cerebral ischemia or thrombosis. Studies of young women without apparent atherosclerosis have shown that hypertension increases the risk for a thrombotic stroke and likewise enhances the effect of oral contraceptives on the occurrence of thrombotic strokes.[129] Studies on the autoregulation of cerebral blood flow[130] suggest that the structural changes in the cerebral resistance vessels caused by hypertension may lead to cerebral ischemia because of the inability of these vessels to dilate in response to a decrease in perfusion pressure. These findings may account for the well known clinical observation that

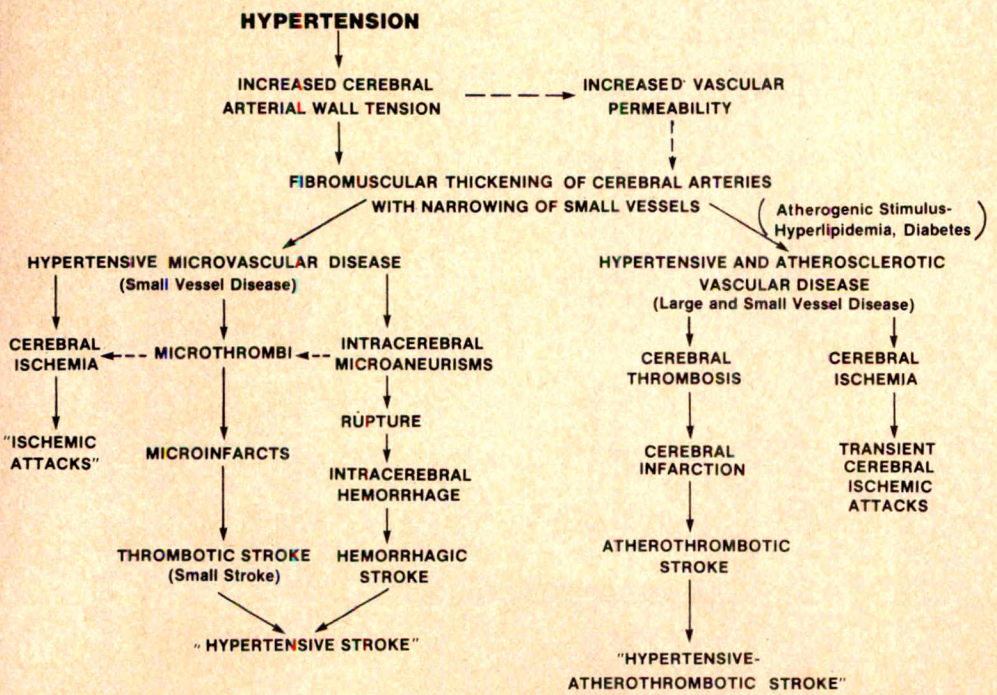


FIGURE 7. Role of hypertension in cerebral vascular disease and stroke.

patients with long-standing hypertension generally do not tolerate a sudden and marked reduction of blood pressure without having symptoms of a reduced cerebral blood flow.

In the presence of hypercholesterolemia the small and large cerebral vessels of subhuman primates with hypertension undergo atherosclerotic changes that, together with the hypertensive changes in the vessels, contribute to the luminal narrowing of the arteries.[7] Similar vascular changes appear to occur in hypertensive patients with cerebrovascular disease and atherothrombotic stroke. In normotensive persons with cerebral atherosclerosis it is distinctly unusual for the cerebral arteries to be significantly involved beyond their first major branching. However, in hypertensive patients the atherosclerosis not only is more severe but also involves smaller vessels that may become thrombosed and result in microinfarcts or small cystic areas of softening called lacunes found especially in the basal ganglia and brain stem.[131] These focal lesions may be responsible for repeated "small strokes" in hypertensive subjects. Diabetes may augment the vascular effects of hypertension because, like hypertension, it is associated with small vessel disease and increased severity of cerebral atherosclerosis.[132,133]

Ruptured aneurysm: Intracerebral microaneurysms, so-called Charcot-Bouchard aneurysms, have been demonstrated at autopsy in close to 50 percent of hypertensive patients.[127] Rupture of these aneurysms is an important cause of intracerebral hemorrhage in hypertensive patients over age 40 and is preventable by effective control of blood pressure with antihypertensive drugs. Small hemorrhages produced by these aneurysms may give rise to clinical manifestations of a stroke that are indistinguishable from those produced by cerebral thrombosis or embolism. The Charcot-Bouchard aneurysm appears to result from destruction of the arterial media by hypertension. Intracerebral microaneurysms have not yet been demonstrated in subhuman primates with hypertension of relatively short duration. However it has been found that stroke-prone spontaneously hypertensive rats with a systolic blood pressure of more than 200 mm Hg do have intracerebral microaneurysms that frequently rupture and cause stroke.[134]

Rupturing of a gross "berry" aneurysm with bleeding into the subarachnoid space is another major cause of stroke and is preventable by control of the blood pressure. These aneurysms, which involve the extracerebral arteries usually in or around the circle of Willis, occur with increased frequency in patients with coarctation of the aorta or with polycystic kidney disease. They are believed to result from a developmental defect in the arterial media and do not seem to occur in animals with surgically produced coarctation of the aorta.

Arteriosclerotic Hypertension and Cardiovascular Disease

Arteriosclerotic hypertension or hypertension associated with arteriosclerotic vascular disease is a major cause of cardiovascular morbidity and mortality in older persons. Little information is available concerning the pathogenesis and treatment of this disease. Arteriosclerotic hypertension is commonly observed in persons over age 60. It appears to be one of the major manifestations of aging and results from arteriosclerotic involvement of the aorta and major arteries. The systolic blood pressure is usually more than 175 mm Hg, whereas the diastolic blood pressure may be normal or slightly increased (less than 110 mm Hg). Many of the patients with elevation of diastolic pressure may give a history of antecedent essential hypertension.

Mechanism: From a conceptional point of view, arteriosclerotic hypertension may be regarded as a primary disease of the musculoelastic media of large and medium-sized vessels that leads to complicating hypertensive cardiovascular disease and atherosclerosis. With aging there is an increase in blood pressure that is associated with a progressive loss of the elasticity of the aorta and other peripheral arteries.[135] Changes in aortic elasticity appear to be related to the calcification of the aortic media, which normally begins after age 10 and gradually increases with age.[136] The role of diet in these arterial changes deserves study in view of the observations that in populations with a small sodium intake the incidence rate of hypertension is low and blood pressure does not increase with advancing years.[137]

Although it is generally believed that the elastic fibers in the aorta serve as the nucleus for calcium deposition, there is growing evidence that calcification in the aortic media is associated with lipid-containing vesicles in the intercellular matrix.[138] These matrix vesicles appear to be derived from the cell membranes of degenerating smooth muscle cells and are the initial sites of calcification of the arterial media. A primary role of matrix vesicles has also been described in the calcification of cartilage and developing bone.[139] Calcification of the arterial media is often accompanied by atherosclerotic involvement of the intima, which accounts for much of the morbidity and mortality in arteriosclerotic hypertension. The increased rigidity of the aorta appears to be responsible for the elevated systolic and pulse pressures of arteriosclerotic hypertension, whereas arteriolosclerosis caused by aging and hypertension could provide an explanation for the increased peripheral vascular resistance reported in this disorder.[140]

Some patients with arteriosclerotic hypertension experience postural dizziness, which may be due to an inability of the cerebral circulation to adjust rapidly to changes in posture or to orthostatic falls in blood pressure. A high as well as a relatively low blood pressure may lead to a "stroke" in such patients or to other manifestations of circulatory insufficiency. The marked fluctuations of blood pressure that occur in arteriosclerosis may be due to hypoactive pressor and depressor reflexes caused by an impairment in autonomic and baroreceptor function. Diabetes, which commonly occurs in arteriosclerotic hypertension,[141] may play a role in both the autonomic and vascular disorders.

Complications: The serious complications of arteriosclerotic hypertension are often due to occlusive disease of the cerebral, coronary and peripheral arteries. Aneurysm formation and rupture of diseased vessels,

articularly in the brain or abdomen, also contribute to norbidity and mortality. When the blood pressure uddenly increases in severity or becomes malignant, therosclerotic occlusion of the renal artery should be uspected as a complication.

Although many of the complications of systolic hypertension in the elderly may be primarily due to atherosclerotic disease, many appear to be precipitated and aggravated by the systolic hypertension itself. These complications include intracerebral hemorrhage and stroke" due to rupture of a Charcot-Bouchard aneurysm and congestive heart failure associated with the systolic overload on the left ventricle.

Therapy: Although the increased morbidity and mortality rates associated with systolic hypertension have been well substantiated, no long-term controlled study has been carried out to assess the efficacy of therapy of arteriosclerotic hypertension. Gradual and cautious moderation of the blood pressure with mild antihypertensive drugs in small doses may be attempted, particularly when diastolic pressure is elevated, because treatment may relieve symptoms and protect against heart failure and "stroke." Sudden and excessive reduction of blood pressure should be avoided because it can precipitate a cerebrovascular accident and other forms of circulatory insufficiency.

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Increased Plasma Catecholamines in High Renin Hypertension

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Plasma catecholamines, indexes of sympathetic nervous tonicity, were measured simultaneously with renin both supine and after standing plus furosemide in patients with primary hypertension and normotensive volunteers. Seventy percent of hypertensive patients with high renin levels had increased catecholamines compared with a 14 percent incidence in the combined group with low and normal renin ($P < 0.001$). Basal catecholamines were related directly to renin in the hypertensive patients and to blood pressure in the normal ($P < 0.05$), but not in the high and low renin subgroups, and inversely to percent increase of catecholamines after standing plus furosemide in hypertensive and normotensive patients ($P < 0.01$). Sympathetic nervous hypertonicity may be responsible for the elevation of blood pressure and for the activation of the renin-angiotensin system in patients with high renin hypertension.

Sympathetic nervous dysfunction may be a factor in the pathogenesis of primary hypertension. Plasma norepinephrine and serum dopamine-B-hydroxylase, markers of sympathetic nervous activity, were increased in some of these patients, as recently reviewed.[1] In this study plasma catecholamines were measured to assess the adrenergic tone of patients with primary hypertension whose renin status was defined by both basal and stimulated renin. The findings indicate adrenergic hyperactivity in some hypertensive patients with high renin levels.

Methods

Informed consent was obtained for studies performed in 66 patients with primary hypertension (28 women and 38 men aged 18 to 72 years) without evidence of sequelae of their hypertension. Comparative studies were performed in 54 normotensive volunteers (19 women and 35 men aged 17 to 51 years). The average age of hypertensive patients was 43 ± 2 and that of normotensive subjects was 33 ± 1 (mean ± standard error). Blacks comprised 16 percent of both normotensive and hypertensive subjects. Patients were not taking antihypertensive medications for at least 1 month prior to this study. No subjects were taking birth control medications. Patients were classified in three categories: *hypertensive*, those with an average of three or more supine blood pressure readings equal to or greater than 140/90 mm Hg; *labile*, those with one or more blood pressure determinations of less than 90 mm Hg diastolic; and *sustained*, those with all diastolic blood pressure readings of 90 mm Hg or greater.

Each of the 120 subjects was instructed to eat a diet containing more than 100 mEq/day of sodium for 3 days before the study. Sodium excretion measured for the 24 hours preceding the study ranged from 100 to 180 mEq. Patients with sodium excretion values outside these limits were excluded from the study. Blood specimens and blood pressures were taken from each subject after 60 minutes of supine rest in the morning after an overnight fast. A sample was taken from 60 patients and 20 normal volunteers on the following morning after they had stood for 60 minutes, 12 hours after oral ingestion of 80 mg of furosemide. Renin and catecholamine responsiveness is expressed as percent increase in their values when measured after standing plus furosemide.

Plasma catecholamines were measured with either the enzymatic method of Engelman et al.[2] or the fluorometric method of Renzini et al.[3] Concentration

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of total catecholamines determined from duplicate specimens of 20 patients with hypertension was similar when analyzed with the two methods.[4] Plasma renin was measured with the radioimmunoassay method of Haber et al.[5] at pH 5.5 with 8-hydroxyquinoline.

The significance of differences between the means was tested with use of Student's *t* test. Linear-regression coefficients were determined with the Olivetti Model 101 calculator. The significance of differences in incidence of increased catecholamines in different renin subgroups was calculated by the chi square test.

Results

Clinical characteristics of the hypertensives: *Renin activity and renin responsiveness* of the 66 hypertensive patients were compared with those of 40 normotensive subjects, 13 women and 27 men. Patients with suppressed responsiveness to orally administered furosemide were characterized as having low renin (that is, stimulated plasma renin activity less than the mean minus 2 standard deviations of the mean of normotensive subjects [2.66 ± 0.72 or 1.2 ng/ml per hour]). Patients were classified as having high renin if supine values were greater than the means +2 standard deviations of the means of the normotensive volunteers (0.48 ± 0.31 or 1.1 ng/ml per hour). Twenty-six (39 percent), 30 (46 percent) and 10 (15 percent) of hypertensive patients were classified as having low, normal or high renin, respectively. Fifty percent of those with low and 20 percent of those with normal renin were black. None of the black hypertensive patients had a high renin level. The average age of the low renin group (49 ± 2 years) was significantly higher ($P < 0.05$) than that of the normal (39 ± 2 years) or the high (41 ± 3 years) renin group. Women comprised 46, 40 and 40 percent, respectively, of the subgroup population.

The mean blood pressures of the low renin group (169 ± 5 systolic, 103 ± 4 diastolic) were greater than those of the other groups (153 ± 4 systolic, 93 ± 2 diastolic for the normal and 156 ± 9 systolic and 96 ± 4 diastolic for the high renin group); only the difference between the low and normal renin groups was significant ($P < 0.05$). The mean blood pressure of normal volunteers was 117 ± 3 systolic and 70 ± 1.5 diastolic.

Catecholamines of hypertensive patients according to renin level: The prevalence rate of increased plasma catecholamines of hypertensive patients was 27 percent when values for male and female subjects were compared with respective normotensive values (Fig. 1). The 70 percent prevalence rate of patients with increased plasma catecholamines in the high renin group was significantly greater than the 14 percent rate in the combined low and normal groups ($P < 0.001$). There was no difference in the prevalence of increased plasma catecholamines between races or between patients with labile or sustained hypertension.

The mean plasma catecholamine level of hypertensive patients was 38 percent greater than that of normotensive subjects ($P < 0.001$) (Table I). The basal plasma catecholamines of male and female hypertensive patients were 246 ± 139 and 338 ± 119 ng/liter, respectively, compared with 167 ± 54 and 280 ± 104 ng/liter in normotensive subjects (mean ± standard deviation). The plasma catecholamine levels of women in both groups were significantly greater than those of men ($P < 0.001$).

Mean plasma catecholamine values of high renin hypertensive patients were nearly twofold greater than those of low and normal renin patients ($P < 0.01$). Basal catecholamine levels of all hypertensive patients were correlated with simultaneous renin determinations ($r = 0.43$; $P < 0.05$). Basal catecholamine values were related to individual blood pressure values of hypertensive patients in the normal renin subgroup only ($r = 0.31$; $P < 0.05$). Catecholamine responsiveness after standing plus furosemide was inversely related to basal plasma catecholamine levels of both normotensive ($r = 0.81$; $P < 0.01$) and hypertensive subjects ($r = 0.48$; $P < 0.01$).

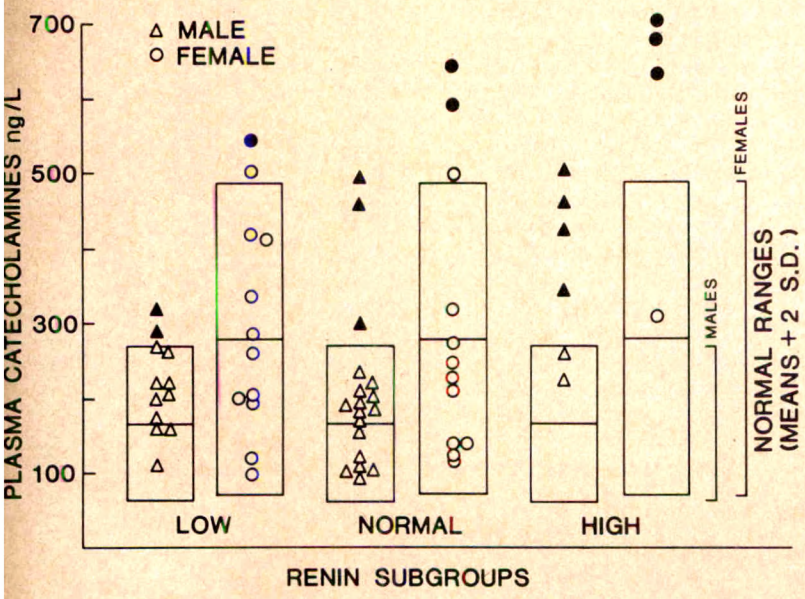


FIGURE 1. Basal plasma catecholamines in hypertensive patients according to renin subgroupings. **Solid triangles** and **circles** (representing values for men and women, respectively) represent plasma catecholamine values greater than 2 standard deviations (S.D.) above the normal means. The two **open circles** shown above the 2 standard deviation boxes for women with low and normal renin hypertension show the normal values corrected for age.

Biochemical and clinical features of hypertensives with raised plasma catecholamines: Blood pressure in patients with increased plasma catecholamines in the low renin group (178 ± 14/117 ± 17 mm Hg) was greater than values (152 ± 10/99 ± 5 and 161 ± 8/91 ± 3 mm Hg) in the normal and high renin groups, respectively. These values were not significantly different from blood pressures of all hypertensive patients by subgroup. Forty percent of patients with increased catecholamines in the normal and low renin groups were black. No patient in the high renin group was black. The prevalence rate of increased plasma catecholamines was similar for both men and women, 17 to 25 percent in the low and normal renin groups and 67 to 75 percent in the high renin group. The mean basal plasma catecholamine values did not differ significantly among patients with increased catecholamines in the various renin subgroups (Table II). Hypertensive patients with increased plasma catecholamine values had 66 percent less catecholamine responsiveness than normotensive volunteers (P <0.001).

Discussion

There was a significantly greater prevalence of increased catecholamines in the high renin group. Our findings of increased mean plasma catecholamines in hypertensive patients further substantiate the data of Louis[6] and Engelman[7] and their co-workers. Previously we reported a 26 percent prevalence rate of increased plasma catecholamines in patients with primary hypertension, equal among male and female patients and those with labile or sustained hypertension. There was a weak correlation between diastolic blood pressure and plasma catecholamines, but the hypertensive subjects of that study were not defined further clinically.[8] We also found a correlation between plasma catecholamines and plasma renin in patients with hypertension.[1]

Renin and primary hypertension: Brunner et al.[9] directed attention to a possible pathogenetic role for renin in primary hypertension when they found greater morbidity in patients with high than in those with low renin hypertension. The percent distribution of our patients into various renin subgroups was similar to that of the study of Brunner et al.,[9] although the criteria for separation into renin subgroups was different. Their patients were classified on the basis of an ambulatory renin determination and the associated 24 hour urinary sodium excretion level. Further, our high renin group included patients with sustained or labile hypertension but no renal sequelae, whereas the high renin group of Brunner et al. had a high prevalence rate of renal insufficiency. Blood pressure in our high renin group was lower than in the patients of Brunner et al.[9] However, the mean blood pressure of our low renin group was higher than that of our normal renin group, thus confirming the findings of Gulati et al.[10]

Plasma catecholamine responsiveness and renin subgroups: The basal plasma catecholamine values of patients in our low and normal renin subgroups were related directly to the inverse of plasma catecholamine responsiveness. Those with the lowest plasma catecholamine values often had the most dramatic responses of catecholamines after standing and furosemide.

TABLE I

Basal Plasma Catecholamines of Hypertensive Patients According to Renin Subgroups (mean ± standard error of the mean)

	Patients (no.)	Supine Renin (ng/ml per hour)	Total Catecholamines (ng/liter)
I. Hypertensive patients			
A. Low renin	26	0.32 ± 0.04 (26)	257 ± 24 (24)
B. Normal renin	30	0.58 ± 0.05 (30)	243 ± 27 (30)
C. High renin	10	1.98 ± 0.22 (10)	454* ± 55 (10)
All hypertensive patients	66	0.69 ± 0.08 (66)	286 ± 21 (64)
II. Normotensive subjects	54	0.48 ± 0.05 (40)	207* ± 12 (54)
P values			
IA vs. IB		<0.001	NS
IA vs. IC		<0.0001	<0.01
IB vs. IC		<0.0001	<0.01
I vs. II		<0.05	<0.01

* The total catecholamines of the high renin subgroup were significantly greater than those of normotensive volunteers (P <0.001).
Figures in parentheses indicate number of patients. NS = no significant difference; P = probability.

TABLE II

Plasma Catecholamines and Catecholamine Responsiveness in Patients With Increased Plasma Catecholamines (mean ± standard error of the mean)

Group	Patients (no.)	Supine Renin (ng/ml per min)	Total Catecholamines (ng/liter)	Percent Change After Standing Plus Furosemide	
				Renin	Total Catecholamine
I. Patients with increased catecholamines	17	1.12 ± 0.23 (17)	511 ± 36 (17)	400 ± 130 (11)	76 ± 24 (11)
II. All hypertensive patients	66	0.69 ± 0.08 (66)	286 ± 21 (64)	409 ± 58 (60)	154 ± 19 (58)
III. All normotensive subjects	54	0.48 ± 0.05 (40)	207 ± 12 (54)	870 ± 200 (18)	162 ± 22 (22)
P values					
I vs. II		NS	<0.0001	NS	<0.02
I vs. III		<0.01	<0.0001	NS	<0.02

Figures in parentheses indicate number of patients studied; NS = no significant difference; P = probability.

Conversely, patients with increased basal plasma catecholamines had smaller increments with sympathetic nervous stimulation. In preliminary studies we have observed the same relation after standing alone. Similarly, serum dopamine-B-hydroxylase of hypertensive patients was stimulated less by standing or standing plus furosemide than in normotensive volunteers with lower levels of basal plasma catecholamines.[11]

There was no general correlation of plasma catecholamines with diastolic or systolic blood pressure in hypertensive subjects except in the subgroup with normal renin. These patients may be similar to those who respond to ganglionic blockade with simultaneous reduction of both plasma catecholamines and blood pressure.[6] Some patients with markedly increased catecholamines had minimal elevation of diastolic blood pressure. On the other hand, patients with slightly increased plasma catecholamines (300 to 400 ng/liter) had a diastolic pressure greater than 120 mm Hg.

Renin and increased sympathetic nervous function: Sympathetic nervous function, as reflected by basal plasma catecholamines, is increased in 30 percent of patients with primary hypertension. We expected to find increased renin in all of our patients with increased catecholamines. However, half of these patients had normal or low renin values. Perhaps other factors, either compensatory mechanisms or those related to magnitude and duration of the hypertension or renal sequelae,[12] account for their blunted renin response. Alternatively, as postulated in renovascular hypertension,[13,14] increased sympathetic tone in patients with high renin levels may be a consequence of an abnormal stimulus to renin production. The latter explanation is not supported by findings of a delay in blood pressure reduction among patients with high renin levels after beta blocking agents despite immediate suppression of plasma renin.[15] Increased sympathetic nervous activity may be responsible for elevated blood pressure in high renin hypertension. Increased renin may be a biochemical marker of sympathetic nervous hyperactivity in high renin hypertensive patients without renal dysfunction.

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New Mineralocorticoids and Adrenocorticosteroids in Hypertension

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Alterations in steroidogenesis have been demonstrated in experimental and human hypertension. It is highly likely that increased secretion of the nonaldosterone mineralocorticoid deoxycorticosterone (DOC) and 18-hydroxy-11-deoxycorticosterone (18-OH-DOC) may initiate or perpetuate hypertension, or both. It is possible that 16 beta-hydroxydehydroepiandrosterone (16β-OH-DHEA) directly induces the hypertensive process in animals. The significance of the findings of increased secretion of 16 alpha,18-dihydroxy-11-deoxycorticosterone (16α,18-diOH-DOC) and dehydroepiandrosterone sulfate (DHEA-S) cannot now be appreciated. Neither has been examined experimentally for its ability to induce hypertension, and the former compound is not a mineralocorticoid. It does possess the curious property of increasing mineralocorticoid activity of other steroids, by altering either their metabolism or mode of action. Variations in the mineralocorticoid hypertensive syndrome or, more aptly, the steroid hypertensive syndrome could account for the hypertension in a substantial portion of patients with reduced plasma renin activity.

Excessive secretion of one or more of at least five nonaldosterone adrenocortical hormones has been observed in certain patients with hypertension. These hormones include deoxycorticosterone (DOC), 18-hydroxy-11-deoxycorticosterone (18-OH-DOC), 16α, 18-dihydroxy-11-deoxycorticosterone (16α, 18-diOH-DOC), 16β- hydroxy dehydroepiandrosterone (16β-OH-DHEA) and dehydroepiandrosterone sulfate (DHEA-S) (Table I).[1–16] Three of these seemingly behave as weak mineralocorticoids; 16α, 18-diOH-DOC may facilitate mineralocorticoid activity but DHEA-S exhibits negligible effects on sodium metabolism, possibly functioning as a biologic marker.

The mineralocorticoid hypertensive syndrome: A concept of the mineralocorticoid hypertensive syndrome has gradually evolved since Conn et al.[1] first described the manifestations of excessive aldosterone secretion in man. The essential features of the syndrome include suppressed plasma renin activity, hypervolemic or volume-dependent hypertension, adrenocortical structural abnormalities and excessive mineralocorticoid secretion. It is well established that repeated injections of aldosterone and deoxycorticosterone into animals and man can produce hypertension,[17,18] and it was recently shown that injections of 18-OH-DOC into rats for 3 weeks induced hypertension.[19] The mineralocorticoid hypertensive syndrome resembles hyporeninemic essential hypertension in several important respects. The most important common characteristic is volume-dependent sustained hypertension. Many patients with the mineralocorticoid hypertensive syndrome or with hyporeninemic essential hypertension respond equally well to diuretic therapy alone, and dramatically to mineralocorticoid antagonists such as spironolactone.[20] Nonaldosterone adrenocortical steroid secretory excess has been observed predominantly in patients with so-called low renin essential hypertension and, by implication, it has been assumed (without sufficient evidence) that these substances initiate, perpetuate

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or intensify hypertension through accepted mineralocorticoid mechanisms. For this reason it is necessary to consider the nature of low renin essential hypertension briefly.

Observations on the nature of low renin hypertension: Numerous studies[20–31] have identified a subgroup of patients who seemingly have essential hypertension but who exhibit suppressed or hyporesponsive plasma renin activity when challenged by any maneuver that will acutely produce substantially negative sodium balance.[21,22] This subpopulation of patients represents approximately 20 to 25 percent of the hypertensive population at large. Interestingly, the only other situation in which untreated patients with hypertension have suppressed plasma renin activity is in the mineralocorticoid hypertensive syndrome. Table II lists the features in low renin essential hypertension that may be common to the mineralocorticoid hypertensive syndrome. The demonstration of increased exchangeable sodium, extracellular fluid and plasma volumes and also the hypotensive effects of sodium deprivation and diuretic therapy in both disorders suggest that increased sodium and water retention is an immediate cause of the volume-dependent hypertension observed. Furthermore, compelling evidence has been obtained to support the idea that adrenal mineralocorticoid excess has a primary role in the genesis of low renin essential hypertension, since Woods et al.[24] were able to reduce the blood pressures of patients with low plasma renin activity by administering aminoglutethimide, an inhibitor of steroidogenesis at an early stage. On the other hand, aminoglutethimide was ineffective in reducing the blood pressures of hypertensive patients with normally responsive plasma renin activity. Gunnells et al.[25] observed obvious structural abnormalities of the adrenal glands in low renin patients undergoing adrenalectomy. Grim et al.[26] reported that all of their low renin patients undergoing bilateral total adrenalectomy became normotensive. Padfield et al.[31] found that patients with low renin essential hypertension had significantly lower exchangeable potassium measurements than hypertensive patients with normally responsive plasma renin activity. Studies in process by Gavras et al.[30] describe failure of low renin hypertensive subjects to respond to inhibition of angiotensin II action by ^{1}sar-^{8}ala-angiotensin (Saralosin®) suggesting preeminence of sodium excess in this form of hypertension.

On the other hand, in some of the studies cited in Table II, conflicting observations coexist regarding exchangeable sodium and plasma volume. Table III lists data[32–34] that militate against the concept that low renin

TABLE I

Adrenocortical Hormones Associated With Hypertension

	Reference
A. Potent mineralocorticoids	
1. Aldosteronism	
Primary, solitary adenoma	Conn et al. 1964[1]
Idiopathic, bilateral nodular hyperplasia	Katz, 1967[2]
Glucocorticoid, remediable	Sutherland et al. 1966[3]
Congenital	Moran et al. 1960[4]
B. Weak mineralocorticoids	
1. Deoxycorticosterone (DOC) excess	Streeten et al. 1969[5]
Idiopathic, nodular hyperplasia	Kahn et al. 1966[6]
(?) isolated	Brown et al. 1972[7]
17α-Hydroxylase deficiency	Biglieri et al. 1966[8]
11β-Hydroxylase deficiency	Eberlein and Bongiovanni, 1956[9]
Ectopic ACTH Cushing's syndrome	Biglieri et al. 1968[10]
2. 18-Hydroxydeoxycorticosterone (18-OH-DOC) excess	
Idiopathic	Melby et al. 1970[11]
Solitary adenoma	Melby et al. 1972[12]
17α-Hydroxylase deficiency	Melby et al. 1972[13]
Ectopic ACTH Cushing's syndrome	Melby et al. 1971[13]
3. (?) 16β-Hydroxy dehydroepiandrosterone (16β-OH-DHEA) excess	Liddle and Sennett, 1974[14]
C. ? Facilitation of mineralocorticoid activity	
1. 16α, 18-Dihydroxydeoxycorticosterone excess (?)	Dale and Melby, 1973[15]
D. Negligible mineralocorticoid activity	
1. Dehydroepiandrosterone (DHEA-S) sulfate	Sekihara et al. 1975[16]

TABLE II

Features of Low Renin Hypertension Resembling the Mineralocorticoid-Hypertensive Syndrome

Finding	Reference
Plasma renin activity unresponsive to sodium depletion	Küchel et al.[21]; Helmer and Judson[22]
Aldosterone-suppressed renin unresponsive to sodium depletion	Helmer and Judson[22]
Plasma aldosterone unsuppressible by sodium	Grim et al.[26]
Increased blood volume	Helmer and Judson[22]
Increased exchangeable sodium	Woods et al.[24]
Increased extracellular fluid volume	Jose et al.[23]
Low salivary sodium/potassium ratio	Crane et al.[27]
Normotensive with adrenal inhibitor	Woods et al.[24]
Characteristic response to spironolactone	Spark and Melby[20]
Structural adrenal abnormalities	Gunnells et al.[25]
Normotensive after adrenalectomy	Grim et al.[26]
Increased central blood volume	Esler et al.[29]
Sodium dependency (response to Saralasin)	Gavras et al.[30]
Decreased exchangeable potassium	Padfield et al.[31]
Increased mineralocorticoid activity of urinary extracts	Sennett and Liddle[28]

TABLE III

Features of Low Renin Hypertension Unlike Mineralocorticoid Excess

Finding	Reference
Normal plasma volume	Schalekamp et al.[32]
Normal extracellular fluid	Schalekamp et al.[32]
Normal exchangeable sodium	Lebel et al.[33]
Normal plasma extract competition for binding to mineralocorticoid receptors not increased	Baxter[34]

hypertension is predominantly a manifestation of mineralocorticoid excess. Displacement of aldosterone from its receptor proteins by products of crude extracts of plasma may not be a valid means of assessing mineralocorticoid activity in the case of very weak mineralocorticoids because of the limitation of plasma sampling.[34] In two studies,[32,33] patients secreting excessive amounts of DOC who exhibited other stigmata of the mineralocorticoid hypertensive syndrome did not have increased values for plasma and extracellular volumes or exchangeable sodium. Comparative hemodynamic studies are lacking for the hypertensive subgroups. The possibility that the low renin state is a stage in the development of essential hypertension and not an entity cannot be excluded in a significant proportion of patients. However, it is tempting to conclude that this subpopulation of patients with low plasma renin activity is afflicted with the mineralocorticoid hypertensive syndrome and that any mineralocorticoids involved have yet to be characterized because of the recent and rapidly accumulating demonstrations of altered adrenal steroidogenesis in the low renin hypertensive population. The roles of the various nonaldosterone adrenocortical steroids, cited in Table I, in human hypertension will be considered in the discussion to follow.

Deoxycorticosterone (DOC) Excess

Administration of deoxycorticosterone acetate (DOCA) to laboratory animals and to man induces sodium retention and potassium loss in urine. Experimental hypertension induced by DOCA has been well studied and an abundant literature lists its characteristics. It has been amply demonstrated that DOCA hypertension is sodium-dependent and will not occur in animals deprived of salt. DOC is predominantly but not exclusively secreted by the zona fasciculata of the adrenal cortex and is largely under the control of adrenocorticotrophic hormone (ACTH). In adrenal regeneration hypertension and in adrogen-induced hypertension in rats, hypersecretion of DOC is the principal determinant of the development of hypertension.

In man, hypersecretion of DOC is apparently associated with the development of hypertension in those with certain inborn errors of cortisol biosynthesis distal to 21-hydroxylation, such as 17α-hydroxylase and 11β-hydroxylase deficiency. In each of these conditions, DOC hypersecretion is associated with elevated plasma ACTH levels. Heightened DOC secretion is often observed in Cushing's syndrome and particularly in Cushing's syndrome associated with ectopic production of ACTH by neoplastic tissue. Sodium-dependent or volume-dependent hypertension and hypokalemia all accompany even modest increments in DOC secretion. Isolated DOC excess was first observed[5,6] in patients with low renin essential hypertension. Subsequently, elevated plasma DOC concentration was observed[7] on repeated examinations of 6 of 20 patients with low renin essential hypertension. These patients also were observed to have intermittent hypokalemia without provocation. Remission of hypertension and hypokalemia was easily accomplished by administration of spironolactone. The nature of the adrenocortical lesion that is responsible for isolated DOC excess has not bee determined in most of the patients studied. However adrenal venography in two of the patients suggested th overproduction of DOC to be bilateral, and radiographi demonstration of multiple nodules has been made.

Radioimmunoassay of DOC in plasma has been in hibited by the poor specificity of antibodies made t DOC. Large screening programs have only recently bee undertaken. No accurate estimate of the prevalence o isolated DOC excess can be made at present. In a fe patients with isolated DOC excess, the administratio of dexamethasone fails to lower plasma DOC concen trations significantly, thus suggesting autonomy o hypersecretion.

18-OH-DOC excess: 18-Hydroxy-11-deoxycor icosterone (18-OH-DOC) was isolated and identified a a naturally occurring steroid from the medium bathin incubated sectioned adrenal glands[35] and later identi fied as the principal corticosteroid product of incubate rat adrenal slices.[36,37] This steroid was first synthesize by Pappo[38] and shown to have weak mineralocorticoi activity. 18-OH-DOC was isolated from human adrena vein blood and its identification established by Melb et al.[11,13] and confirmed by others.[39,40] In healthy adul subjects,[12] the secretion of 18-OH-DOC was found t be quantitatively similar to the secretion rates of aldo sterone and DOC. Melby et al.[12] provided indirect evi dence in man, dog and rat that 18-OH-DOC is mainl a secretory product of the zona fasciculata of the adrena cortex and that 18-OH-DOC is primarily ACTH-de pendent. Small increments in its secretion could b associated with activation of the zona glomerulosa b sodium depletion. However, in animals and man, ar giotensin evokes no increase in 18-OH-DOC secre tion.

18-OH-DOC in experimental hypertension: Birming ham et al.[41] first demonstrated excessive secretion of 18 OH-DOC using incubated sections of regenerating adrena glands after the development of adrenal regeneration hype tension by adrenal enucleation. These findings were late confirmed in our laboratory.[12,42] In a series of studies, it wa demonstrated that the secretion of all steroids into the adrena venous effluent of rats with adrenal regeneration hypertensio was greatly decreased within 24 hours of the enucleation. DO secretion began to increase 1 week after enucleation and re turned to near control levels by 3 weeks. 18-OH-DOC secre tion was greatly diminished during the first 3 weeks, but th steroid was greatly oversecreted in the 3 weeks after enu cleation. Corticosterone secretion returned to normal at weeks, and aldosterone secretion remained low throughou the study, but it must be recalled that these animals are in gesting large amounts of sodium chloride. These studies o direct adrenal secretion of steroids suggest that conflictin previous studies may merely reflect sampling or experimenta procedures carried out at different times during the deve opment of adrenal regeneration hypertension. 18-OH-DO excess is present at 6 weeks and restoration of DOC secretio is obvious by 3 weeks.

Peripheral steroid levels obtained in the basal or un stressed state in rats during the development of adrenal re generation hypertension confirmed the suspicions arouse by the adrenal venous effluent data that both DOC and 18 OH-DOC were involved in the production of adrenal regen eration hypertension. Gaunt et al.[43] have clearly demonstrate

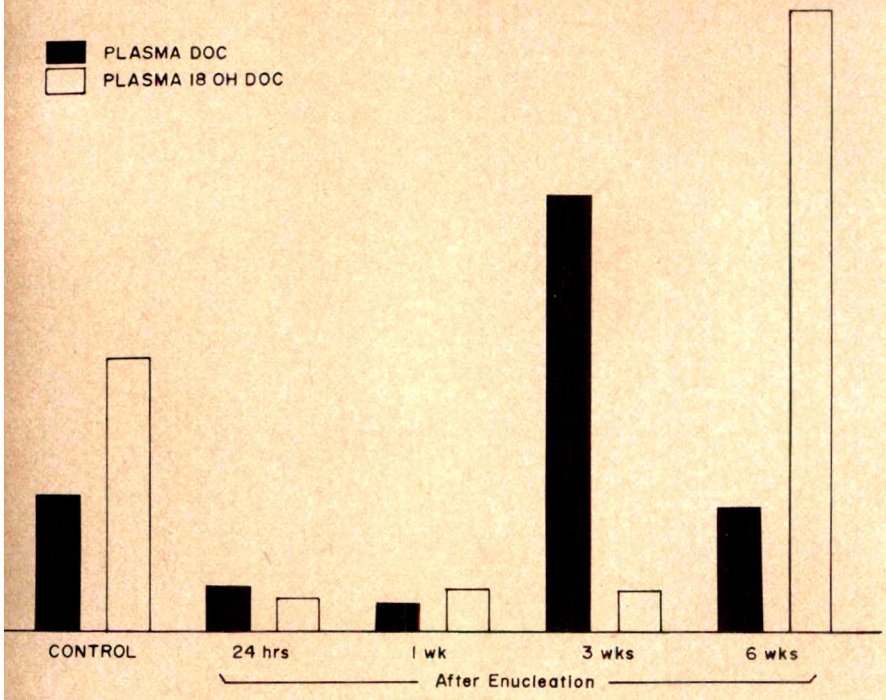


FIGURE 1. Peripheral levels of plasma deoxycorticosterone (DOC) and plasma 18-OH-DOC during the development of adrenal regeneration hypertension after enucleation.

hat basal peripheral DOC levels are at least 10-fold greater n animals with enucleation compared with control animals weeks after enucleation (Fig. 1). At this time the animals are rankly hypertensive. It should be pointed out that DOC levels egin to increase in the peripheral blood at about 2 weeks; 8-OH-DOC levels in the peripheral blood are greatly inreased at 6 weeks, whereas DOC levels are greatly increased t 3 weeks. Since significant hypertension is clearly evident y 3 weeks in these animals, at a time when peripheral DOC oncentrations are markedly elevated, it is highly likely that his is the inciting steroid for the onset of hypertension. It is qually likely that excessive secretion of 18-OH-DOC peretuates and worsens adrenal regeneration hypertension at time when all other mineralocorticoid secretion is, if anyning, suppressed. The amount of 18-OH-DOC secreted after nucleation in the rat with adrenal regeneration hypertension xceeds by far the amount necessary to produce hypertension y injection of exogenous 18-OH-DOC.

Hypersecretion of 18-OH-DOC was demonstrated[44] in some olonies of rats with hereditary hypertension—rats genetically isceptible to salt-induced hypertension when compared with its resistant to the effects of salt on blood pressure. Even hough the mineralocorticoid activity of 18-OH-DOC is iodest in comparison with that of aldosterone, the former has een reported[19,45] to produce hypertension when injected into nmature rats in a dose equivalent to the dose of deoxycortiosterone that produced hypertension. Administration of 8-OH-DOC (in a dose of 200 μg/day) can induce the hyperensive state in the rat within 2 weeks. There is little doubt hat this steroid may play an important role in certain forms experimental hypertension and that modest increments in s secretion are capable of inducing hypertension.

18-OH-DOC excess in human hypertension: Melby et al.[12] demonstrated excessive secretion of 8-OH-DOC in four forms of hypertension, three of hich are associated with suppression of plasma renin ctivity. In 17α-hydroxylase deficiency, Cushing's ndrome, primary aldosteronism and in a small numer of patients with essential hypertension and suppressed plasma renin activity, there was excessive secretion of 18-OH-DOC or of its urinary metabolite 18-hydroxy-tetrahydro-deoxycorticosterone (18-OH-TH-DOC).

The isolation and identification of 18-OH-DOC in human adrenal venous effluent coincided with the growing indirect evidence that suppressed plasma renin activity hypertension might be due to a mineralocorticoid, the structure of which was unknown. The possibility that 18-OH-DOC may somehow be involved in hypertension induced by suppressed plasma renin activity has been examined in large numbers of patients.

We had previously reported[12] that 18-OH-DOC secretory excess was found to be the sole steroid abnormality in approximately 10 percent of hypertensive patients with suppressed plasma renin activity. We have now studied a much larger group of hypertensive patients in terms of their 24 hour urinary excretion of the principal metabolite of 18-OH-DOC, 18-OH-TH-DOC. In normal subjects, the mean excretion of this metabolite is 15.3 μg/day (range 5 to 25 μg/day). Comparative studies in patients with and without hypertension and altered plasma renin activity are shown in Figure 2. The mean 18-OH-TH-DOC excretion in hypertensive subjects with normally responsive plasma renin activity was 13 μg/day. Eighteen percent of 43 of these patients had urinary 18-OH-TH-DOC secretion in excess of the normal range. In patients with low renin essential hypertension or hypertension induced by suppressed plasma renin activity, there appears to be a bimodal distribution of excretion of the 18-OH-DOC metabolites. This bimodal distribution was not apparent in our previous studies, in which the number of patients examined was much smaller. It is probably not valid to report a mean of 44 μg/day with such a bimodal distri-

bution. In more than 40 percent of 114 patients values were above the mean normal range. About 40 percent of the 37 patients with primary aldosteronism exhibited clearly increased 18-OH-TH-DOC excretion. We found no correlation between this increased excretion and the pathologic findings in primary aldosteronism whether or not a solitary aldosterone-producing adenoma was removed or idiopathic hyperaldosteronism or bilateral nodular hyperplasia was demonstrated. In the past 5 years, we have identified increasing numbers of patients with hypertension induced by suppressed plasma renin activity secreting excessive amounts of 18-OH-DOC. The reasons for this are not clear but more than likely result from patient selection. A high percentage of the patients described here exhibited hypokalemia. Several were at first thought to have primary aldosteronism. It is likely that differences in patient selection may account for the apparently contradictory studies of Messerli et al.[40] and Genest et al.[46] in which elevated aldosterone secretion rates were found in patients with essential hypertension and elevated 18-OH-DOC secretion rates were found more often in patients with essential hypertension and normally responsive plasma renin activity. We have observed elevated plasma 18-OH-DOC levels in some hypertensive patients with normal plasma renin activity.

Eighteen patients with suppressed renin hypertension and excessive 18-OH-DOC secretion have been studied in terms of spironolactone responsiveness, aldosterone secretion rate and response of the blood pressure to suppressive doses of dexamethasone. Ten patients (55 percent) exhibited a significant reduction in diastolic blood pressure when given dexamethasone, 1.5 mg/day for 6 weeks. All of the patients had a significant reduction in urinary 18-OH-TH-DOC while receiving dexamethasone. Sixteen of these 18 patients had significant reductions of blood pressure or became normotensive after 3 weeks of large dose spironolactone therapy 400 mg/day. The aldosterone secretion rates in these subjects tended to be low, averaging 80 μg/day. It

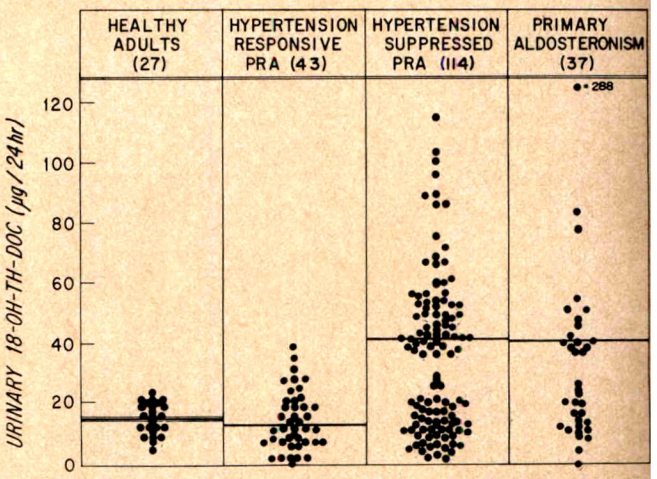


FIGURE 2. Urinary excretion of 18-hydroxy-tetrahydro-deoxycorticosterone (18-OH-TH-DOC) in patients with hypertensive disorders and healthy subjects. PRA = plasma renin activity. Figures in parentheses indicate number of subjects.

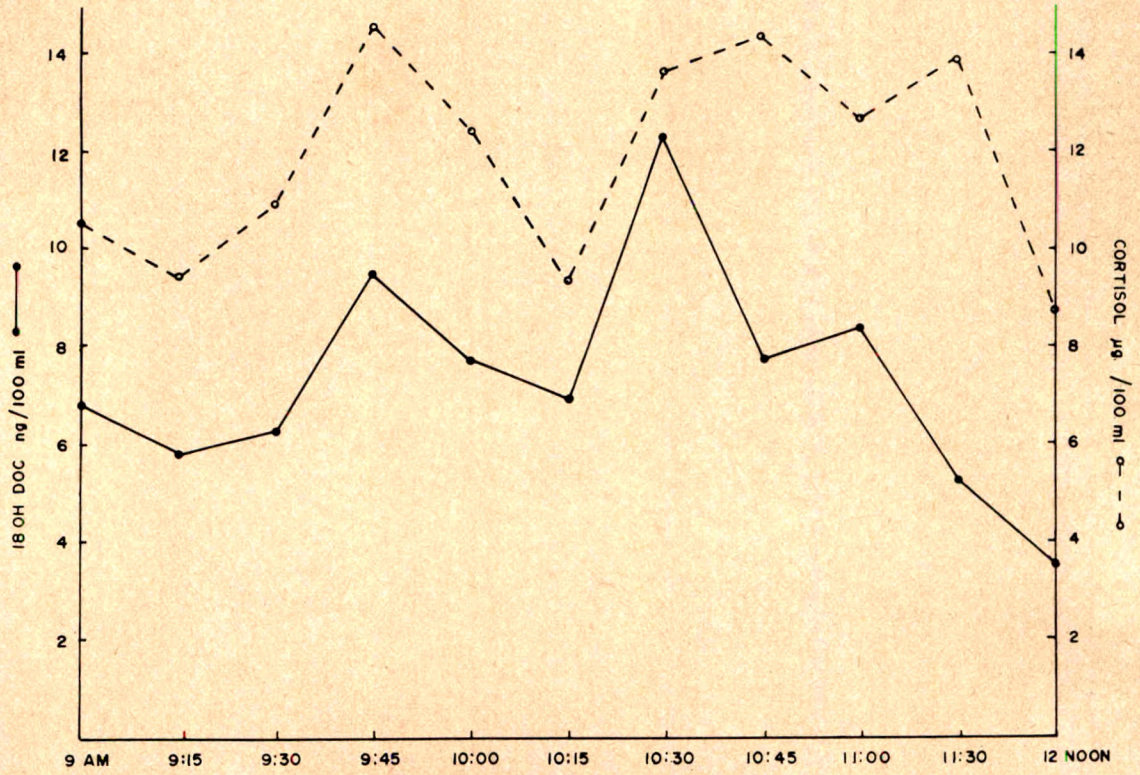
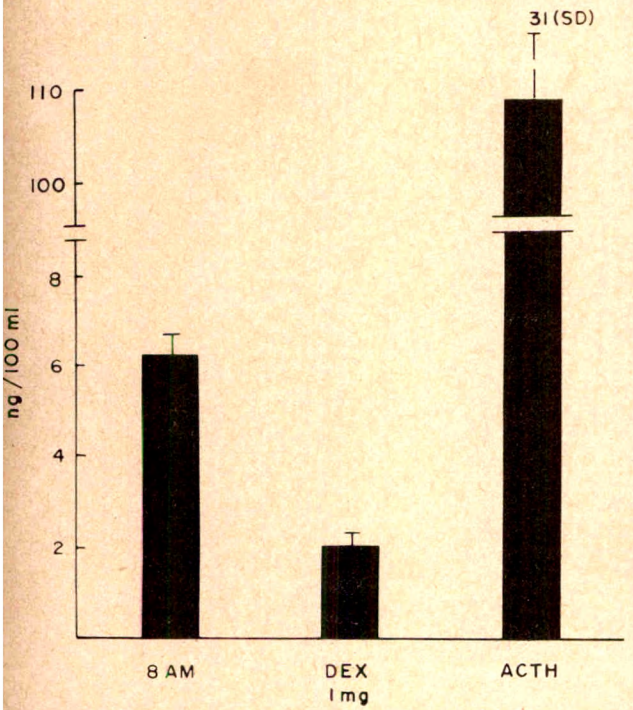


FIGURE 3. Ultradien variation in plasma 18-OH-DOC and cortisol concentrations in one healthy subject.

s difficult to interpret lack of blood pressure responiveness in such patients. The long mineralocorticoid xcess can result in permanent hypertension in some atients. It should be recalled that no more than 70 ercent of patients with primary hyperaldosteronism espond to unilateral adrenalectomy with removal of the denoma and with a normalization of blood pressure.

In summary, a significant increase in secretion of 8-OH-DOC, as reflected by urinary 18-OH-TH-DOC xcretion, occurs in certain proportions of patients with uppressed plasma renin activity hypertension. It is ossible, though not proved, that 18-OH-DOC excess ay play a role in the genesis of hypertension in these atients.

Screening for 18-OH-DOC excess (concentration f 18-OH-DOC in peripheral blood of man): Dale et l.[47] measured peripheral blood levels of 18-OH-DOC sing a sensitive and accurate radioimmunoassay method. The normal concentration in plasma is 5.9 ± 3.4 ng/100 ml in specimens obtained between 8 and 9 AM. The highest levels are expected during this time period, since 18-OH-DOC secretion is primarily under the control of ACTH.[12] The latter greatly increases 18-OH-DOC levels in both peripheral and adrenal venous blood. The concentration in plasma before and after administration of ACTH measured by radioimmunoassay agrees closely with values calculated indirectly from the secretion and metabolic clearance rate data.[12] A marked stimulation by ACTH indicates that 18-OH-DOC may be secreted in pulses similar to those shown for cortisol and may exhibit a so-called ultradien rhythm. Measurement of 18-OH-DOC concentrations in peripheral blood in normal human subjects show that levels vary severalfold during the morning hours (Fig. 3).



IGURE 4. Plasma 18-OH-DOC concentrations in normal subjects t 8 AM, at 8 AM after administration of 1 mg of dexamethasone (DEX) t 11 PM on the previous night, and after 250 μg of 1–24 β corticotropin ACTH). SD = standard deviation.

The suppression and stimulation of plasma 18-OH-DOC concentrations by the administration of dexamethasone and ACTH is indicated in the histogram in Figure 4. The controlled blood samples were obtained at 8 AM and, immediately thereafter, 250 μg of 1–24β corticotropin was administered intravenously. Two hours later blood samples were obtained. Dexamethasone, 1 mg, was administered at 11 PM and an additional blood specimen was drawn the following morning. It can be seen that dexamethasone decreased 18-OH-DOC from control levels of 6.1 ± 1.7 (mean ± standard deviation) to 2.3 ± 0.8 ng/100 ml. ACTH stimulation resulted in an 18-fold increase in levels to 109 ± 31 ng/100 ml in plasma.

Plasma 18-OH-DOC determinations have been made in a small number of hypertensive patients.[47] Basal plasma 18-OH-DOC concentration at 8 AM was clearly elevated in 3 of 16 hypertensive patients with normally responsive plasma renin activity. Williams et al.[48] found 3 of 14 hypertensive patients with normally responsive plasma renin activity to have significantly elevated plasma 18-OH-DOC concentrations; in low renin subjects, such significant elevations were not observed. Because of the ultradien rhythm, it may be necessary to obtain serial measurements of plasma 18-OH-DOC concentrations to assess the significance of casual single determinations. Large hypertensive populations could be screened, and the extent of hypersecretion, alterations in regulation and role of 18-OH-DOC in hypertension could be determined more fully.

16α, 18-diOH-DOC excess: 18-OH-DOC is a relatively weak mineralocorticoid in comparison with aldosterone. We therefore wondered whether it functions as a biological marker in hypertensive patients and is not an end product of steroidogenesis in the human but rather a precursor of a more active mineralocorticoid. The analogy immediately suggested

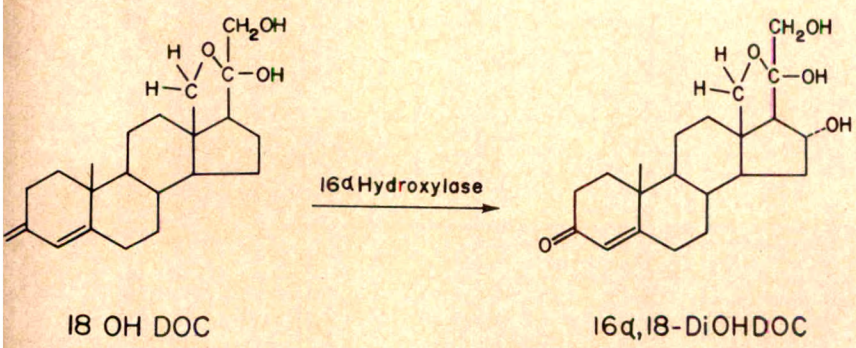


FIGURE 5. Precursor role of 18-OH-DOC in the adrenal fasciculata. 18-OH-DOC is the substrate for 16α-hydroxylase for the formation of 16α, 18-diOH-DOC.

was the precursor relation of 18-hydroxycorticosterone (18-OH-B) to aldosterone. The conversion of 18-OH-B to aldosterone by the action of an 18-hydroxy steroid dehydrogenase in the glomerulosa would be analogous to the conversion of 18-OH-DOC to a hypothetical 11-deoxyaldosterone in the zona fasciculata. Human adrenal incubation studies[49] with radioactive 18-OH-DOC demonstrated efficient conversion to 18-hydroxycorticosterone and less efficient conversion to aldosterone. Radiochromatographic scans of paper chromatograms demonstrated significant conversion to a substance more polar than 18-OH-B. This material was subsequently identified by Dale and Melby[15] to be 16α, 18-dihydroxy-11-deoxycorticosterone (16α, 18-diOH-DOC) (Fig. 5).

To evaluate the biologic action of 16α, 18-diOH-DOC, Dale and Melby[50] studied its effect on sodium retention in the adrenalectomized rat. The histogram in Figure 6 (open bars) indicates that the compound was without effect on sodium metabolism in the rat. Preliminary but subsequently unconfirmed work by Funder of Melbourne, Australia, suggested increased binding of labeled aldosterone to its rat kidney cytosol receptor in vitro in the presence of 16α, 18-dihydroxydeoxycorticosterone. To evaluate the biologic action of the latter in vivo, we studied the effect of this compound on enhancing the sodium-retaining ability of subthreshold doses of aldosterone in the rat; and the conversion of labeled 18-hydroxy-deoxycorticosterone to the compound by adrenal tissue from patients with essential hypertension and low plasma renin activity. An example of the results of this type of experiment is seen in Figure 6. The black bar represents sodium excretion after 50 ng of aldosterone is given (a subthreshold effect). Aldosterone is without significant effect. When 16α, 18-diOH-DOC is given, there is a significant reduction of sodium excretion in response to aldosterone suggesting that somehow it facilitates aldosterone action.

The mechanism by which 16α, 18-dihydroxy-deoxycorticosterone enhances aldosterone activity has not been characterized. Its presence could produce conformational changes in inactive aldosterone cytosol receptors resulting in formation of receptors capable of binding aldosterone. Removal of active receptors by complexing with aldosterone should favor formation of more active receptors. The existence of higher concentrations of aldosterone receptors in target tissues responsible for sodium conservation seems to support the concept that formation of an aldosterone-receptor complex is a prerequisite for expression of aldosterone's metabolic effect. The net effect of 16α, 18-dihydroxydeoxycorticosterone would be to increase the physiologic action of the existing concentration of aldosterone. Another explanation might be that it may retard aldosterone metabolism by the liver and kidney. This possibility has not been thoroughly examined.

The conversion of [1,2-^{3}H]-18-OH-DOC to 16α, 18-dihydroxydeoxycorticosterone was studied in normal adrenal slices and adrenal slices from the low renin essential hypertensive patients. Normal adrenal tissue converted a mean of 15 percent of the added labeled 18-OH-DOC to the 16α metabolite, while conversion of 64 percent was observed in the hypertensive patients. Hypersecretion into the medium was observed to have occurred in patients' incubations relative to normal adrenal incubations, as estimated by ultraviolet absorption on thin layer plates and paper chromatograms.

Increased production of this steroid by adrenal tissue has been demonstrated in our laboratory in vivo as well as in vitro in patients with low renin hypertension. Estimated secretion of 16α, 18-diOH-DOC is one and a half to two times that of 18-OH-DOC but may be as much as fivefold.

16β-OH-DHEA excess: Liddle and Sennett[14,28] found increased excretion in urine of the C-19 steroid

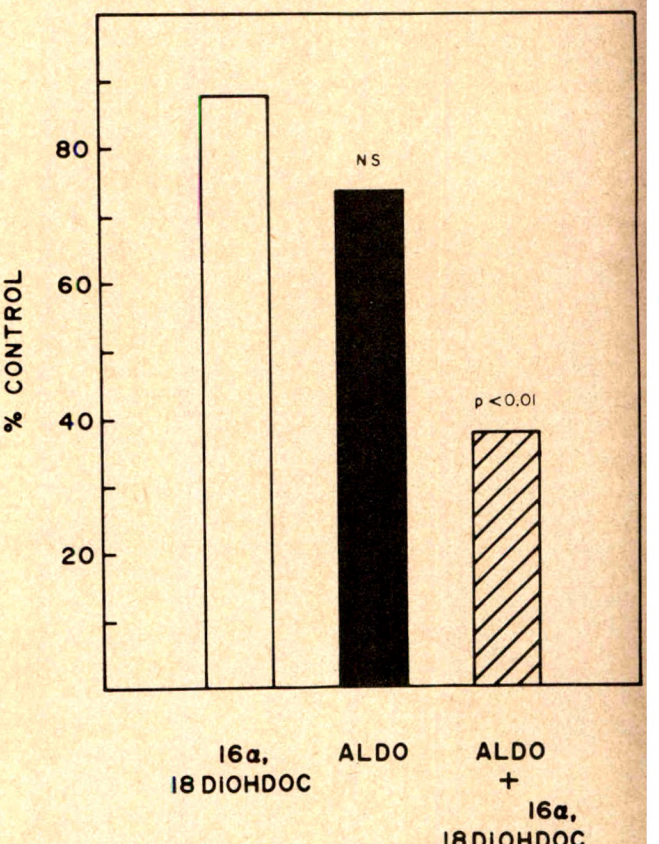
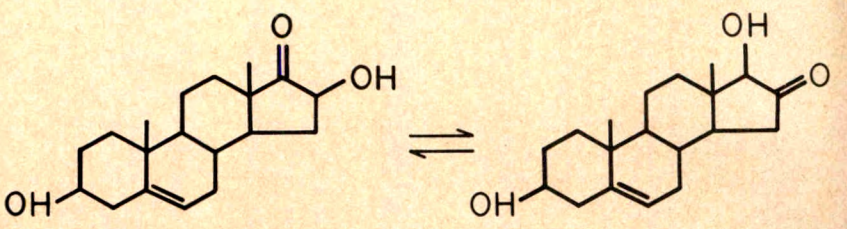


FIGURE 6. Effects of 16α, 18-diOH-DOC, aldosterone (ALDO) and aldosterone plus 16α, 18-diOH-DOC on urinary sodium excretion in the adrenalectomized rat. Probability (p) values are in relation to control data. NS = not significant.



16β-OH-DHEA 16-OXO-ANDROSTENEDIOL

FIGURE 7. C-19 16β-hydroxylated steroids from urine.

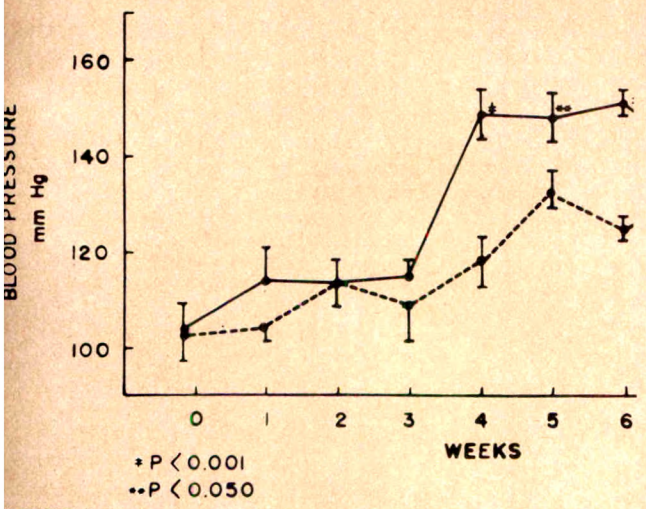


FIGURE 8. Mean arterial blood pressure data in uninephrectomized immature rats after implantation of Silastic capsules of 16β-OH-DHEA **(solid line)** and in control rats **(dashed line).** Bars indicate standard error of the mean.

16β-OH-dehydroepiandrosterone (16β-OH-DHEA) in most of 15 patients with suppressed plasma renin activity and hypertension, and no significant increase in excretion of this steroid in all but 1 of 14 patients with essential hypertension and normally responsive plasma renin activity. In a series of arduous experiments, these investigators demonstrated that the urine of patients with low renin essential hypertension contained greater extractable mineralocorticoid activity than could be accounted for by the presence of any known mineralocorticoid. They assessed the mineralocorticoid activity of extracts by injecting them into adrenalectomized animals and observing the effect on sodium excretion. It was soon found that excess mineralocorticoid activity in the low renin patients could be attributed to the overabundance of the steroid 16β-OH-DHEA and its isomer 16-oxo-androstenediol. These steroids (Fig. 7) were obtained after acid hydrolysis of urine and then extracted. It was found that 16β-OH-DHEA and its 16-oxo isomer exhibited sodium-retaining activity in adrenalectomized rats. All of the patients they examined with low renin "essential" hypertension excreted substantially more than 100 μg/day of 16β-OH-DHEA. More than 95 percent of patients with normally responsive plasma renin activity excreted less than 100 μg/day of the steroid, whereas excessive excretion of this steroid could be demonstrated in all the patients with low renin essential hypertension.

The significance of such provocative observations is not entirely clear. It is not known whether secretion of 16β-OH-DHEA or its precursor DHEA is altered. It is possible that the increased urinary excretion of this metabolite reflects increased hepatic metabolism of DHEA. The next information needed is whether this steroid itself is responsible for increased mineralocorticoid activity or whether it functions as a biologic marker for some more potent but as yet unidentified steroid. Funder et al.[51] have shown only negligible affinity for mineralocorticoid receptors in vitro, and others have not found significant sodium retention induced by this steroid. Shackleton et al.[52] found greatly elevated amounts of 16β-OH-DHEA in the urine of newborn infants who were not hypertensive. Komanicky and Melby[53] implanted Silastic® capsules containing 16β-OH-DHEA under the skin of young uninephrectomized rats and observed a significant increment in blood pressure within 4 weeks (Fig. 8). Permanent hypertension was not achieved during this experiment because the rate of disappearance of 16β-OH-DHEA from the Silastic capsule was rapid when compared with that in DOCA hypertensive control animals. It may be that exposure to the hypertensive stimulus was not sufficient. The increase in blood pressure was highly significant when compared with control values at 4 weeks, and it is concluded that 16β-OH-DHEA does possess a hypertensinogenic activity. It is of interest that a steroid of negligible or barely perceptible mineralocorticoid activity could induce alterations in the blood pressure over this short period. If 16β-OH-DHEA can produce hypertension without sodium retention, then these studies may have implications for the understanding of steroid-mediated hypertension.

DHEA-S Excess

In 1975, Sekihara et al.[16] demonstrated, that in patients with essential hypertension, levels of dehydroepiandrosterone sulfate (DHEA-S) were significantly higher than in the control age-matched group. These findings are of some interest because of the possible precursor role of DHEA-S for 16β-OH-DHEA-S.

It may well be that, in the patients studied by Sennett et al.,[28] DHEA-S levels were also elevated. DHEA-S is not known to be capable of producing hypertension in animals or man, but studies of this notation have not been systematically made. DHEA-S is the most abundant secretory product of the adrenal cortex. Secreted by the adrenal glands, it appears not to be primarily under the control of ACTH.[54] The regulation of the secretion of DHEA-S may be pituitary-dependent, because administration of dexamethasone can ultimately reduce the adrenal secretion of this material. Shao et al.[55] previously reported that the secretion of both DHEA-free alcohol and DHEA-S were increased in hypertensive patients. Classification of the significance of these observations must await additional study.

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Adrenocortical Factors in Hypertension

I. Significance of 18-Hydroxy-11-Deoxycorticosterone

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Low renin essential hypertension and the syndrome of mineralocorticoid excess have two features in common, low plasma renin activity and volume-sensitive hypertension. The proposal that both disorders share a common mechanism—because of the ability of agents that inhibit or antagonize the adrenocortical secretion to lower blood pressure in the low renin hypertensive group—appears to be based on a circular argument. The beneficial effect of removal or neutralization of the adrenocortical contribution only constitutes evidence for volume-dependency or sensitivity, which is how the low renin group is defined. Any measure that blocks a component of the normal homeostatic chain for the maintenance of extracellular and intravascular volume including the adrenal cortex would be expected to have a beneficial effect in volume-sensitive hypertension. Evidence for an adrenal factor in low renin hypertension must rest on the isolation of an active substance that reproduces the effect when readministered. 18-Hydroxy-11-deoxycorticosterone (18-OH-DOC) does not meet these criteria. It is not significantly increased in experimental hypertension and, although its overproduction in unselected low renin essential hypertensive patients remains controversial, the magnitude of the reported elevations is insufficient in relation to the low biologic activity of the steroid to account for a significant effect.

Apart from its increase in the 17α-hydroxylase defect, 18-OH-DOC is increased in primary aldosteronism and may also be an indicator of a histologic variant of the aldosteronoma. On the basis of a large body of evidence showing parallelism between the 11β- and 18-hydroxylase functions of the fasciculata zone, we have proposed that both enzymic functions are functionally related and may involve the same enzyme protein and catalytic site. According to this view, the secretion of 18-OH-DOC would have no special significance of its own but would be an obligatory consequence of the secretion of fasciculata zone corticosterone.

The adrenal cortex secretes two groups of biologically active steroid hormones, the mineralocorticoids and glucocorticoids, and each increases blood pressure by a predominantly different mechanism. The action of the mineralocorticoids, aldosterone and 11-deoxycorticosterone (DOC),* is sodium-dependent in contrast to that of the glucocorticoids.[1] The mechanism of glucocorticoid hypertension, as seen, for example, in Cushing's syndrome due to excessive cortisol secretion or after large dose steroid therapy, is less well understood, but appears to involve more of an effect of the steroid on the vasoconstrictor[2] than on the volume component of blood pressure regulation.[3] The ability of glucocorticoids to increase the synthesis of renin substrate may be another hypertensive mechanism.[4]

Is there an adrenocortical factor in low renin hypertension? The hypertensive syndromes, summarized in Table I, in which adrenocortical hormones have a clearly demonstrated etiologic role, together represent

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* Accepted trivial names of steroids have been used or defined in the text. Compound B is corticosterone, compound S is 11-deoxycortisol. Tetrahydro derivatives refer to the 3α-hydroxy-5β-pregnane configuration.

only a small fraction of the hypertension problem. Several lines of indirect evidence have suggested the participation of the adrenal cortex in a larger fraction of the hypertensive population. The 1 percent prevalence rate of adrenocortical hyperplasia in hypertensive patients seen at autopsy[5] is appreciable in view of the prevalence of hypertension. Low plasma renin activity is found in primary aldosteronism[6,7] and in approximately 20 to 30 percent of patients with benign essential hypertension[8–11] without evidence of overproduction of known mineralocorticoids. The ability of adrenal inhibitors or antagonists to lower blood pressure in patients with low renin hypertension has been cited[12,13] as evidence for the secretion of unknown adrenal factors.

Thus, certain analogies can be drawn between the syndromes of mineralocorticoid excess and low renin hypertension, especially if the latter is defined operationally in terms of the sensitivity of blood pressure reduction to volume depletion. But an analogy between the two syndromes does not establish a common mechanism. If the blood pressure is especially volume-sensitive in the low renin group, any measure that acts on the components of the homeostatic chain that maintain intravascular volume, such as the adrenal cortex, the kidney and sodium balance, would affect blood pressure. Thus, reduction of blood pressure by steroid antagonists or inhibitors in patients with low renin hypertension does not constitute evidence for the operation of another adrenal factor because these agents need only act on the normal components of sodium homeostasis to exert a beneficial effect. Proof of the existence of another adrenocortical steroid mechanism must rest on the demonstration of the presence of a biologically active substance and the administration of that substance to reproduce the effect.

18-Hydroxy-11-deoxycorticosterone (18-OH-DOC): This is one of the steroids suggested to have a role in experimental and human hypertension. Interest in this steroid appears initially to have been prompted by its structural resemblance to aldosterone and 18-hydroxycorticosterone. It was first identified in adrenal incubates by Kahn et al.,[14] synthesized by Pappo[15] and identified as a major corticosteroid in the rat adrenal gland by Birmingham and Ward[16] and Péron.[17] In the rat, 18-OH-DOC arises from the fasciculata zone of the adrenal cortex[18,19] and is adrenocorticotropic hormone-(ACTH)-dependent.[20] In man, 18-OH-DOC is much less abundant, and the normal rate of secretion of approximately 100 μg/day is also stimulated by ACTH.[21,22] 18-OH-DOC is not an important precursor of aldosterone[23] since it arises in a zone that lacks the terminal oxidase mechanism for aldosterone synthesis. As will be discussed, its very low biologic activity appears to preclude an important biologic effect. Thus it is not entirely clear why 18-OH-DOC has been singled out from among all the secretory and metabolic products of the adrenal cortex and steroid-producing organs for extensive investigation. We will attempt in this paper to evaluate critically the role of 18-OH-DOC and the evidence for its participation in experimental and human hypertension.

TABLE I

Adrenocortical Hypertensive Syndromes

Aldosterone excess
Primary aldosteronism due to adenoma
Idiopathic hyperaldosteronism due to bilateral hyperplasia
Dexamethasone-suppressible hyperaldosteronism
DOC (11-deoxycorticosterone) excess
17α-hydroxylase defect
11β-hydroxylase defect
Ectopic ACTH syndrome
Glucocorticoid excess
Cushing's syndrome (cortisol excess)
Large dose steroid therapy

Biologic Activity of 18-OH-DOC

Sodium-retaining activity: Reliable data on the sodium-retaining activity of 18-OH-DOC has been available since 1962, when Kagawa and Pappo[24] found 8 percent of the sodium-retaining activity of 11-deoxycorticosterone (DOC) in the adrenalectomized rat. If DOC is considered to have 4 percent of the activity of aldosterone,[25] these data would be in agreement with more recent work, using rat kidney cytoplasmic mineralocorticoid receptors, in which Feldman and Funder[26] found that aldosterone had approximately 70 times the binding affinity of 18-OH-DOC. Birmingham et al.[27] reported that only one dose yielded sodium-retaining potency equal to that of deoxycorticosterone acetate (DOCA) in the adrenalectomized rat. The statistically more significant result was the effect on sodium/potassium ratio, where the potency was 25 percent that of DOCA, a result similar to that obtained by Gotshall and Davis[28] in the adrenalectomized dog. In both species the effect on sodium retention was somewhat greater than on potassium excretion. The effect of 18-OH-DOC on sodium transport as measured by the short-circuit current in the toad urinary bladder[29] was one fifth that of DOCA.

Glucocorticoid activity: Although there appears to be no data on the effect of 18-OH-DOC in the hepatic glycogen deposition assay, other evidence from receptor binding affinity studies indicates that its glucocorticoid activity is also quite low. Feldman and Funder[26] found less than 1 percent of the binding affinity of corticosterone to rat kidney glucocorticoid receptors, and Ballard (Ballard PL, unpublished data) found less than 0.5 percent of the binding affinity of cortisol in the rat hepatoma and human fetal lung glucocorticoid receptors. In another measure of glucocorticoid activity, the ability to suppress ACTH, 18-OH-DOC was inactive.[30]

Other possible steroid hypertensive mechanisms: Although it is generally assumed that steroids exert a hypertensive effect in relation to their activity as either mineralocorticoids or glucocorticoids, pressor effects not proportional to these activities may be possible. In a preliminary report,[31] pharmacologic doses of 18-OH-DOC increased blood pressure without producing hypokalemia. In rats sensitized by unilateral nephrectomy and saline treatment, hypertension was produced after several weeks at doses of 2 mg[32] and 10 mg/kg,[33] doses that in man would be equivalent to 1,000 to 5,000 times the normal rate of secretion.

Australian investigators[34,35] have described an interesting experimental model in which sheep rapidly become hypertensive when given ACTH. The mechanism is not mineralocorticoid in the usual sense because the hypertension develops within 24 hours and occurs without change in external sodium

balance or body weight. In addition, sheep do not have the syndrome of mineralocorticoid hypertension when given sodium-retaining steroids. The hypertensive effect of ACTH could not be reproduced by reinfusing known components of the adrenal venous effluent singly or in combination. The hypertensive mechanism is unclear but was presumed to result from the stimulated secretion of an unknown adrenocortical factor. A recent preliminary report[36] indicates that this factor is 17α,20α-dihydroxy-4-pregnene-3-one. Certain childhood hypertensive syndromes resemble this model in that ACTH also produces a rapid pressor effect.[37,38]

Possible synergistic effects: Dale and Melby[39] reported the metabolism of 18-OH-DOC to a 16α-hydroxy derivative in vitro in the adrenal tissue from two hypertensive subjects. Data are insufficient to permit any conclusion about the uniqueness of this pathway in hypertension, but these authors[40] report that a 100 to 200-fold molar excess of this metabolite enhances the activity of aldosterone in the adrenalectomized rat bioassay. There has been no systematic examination of the ability of large excesses of other steroids to alter the in vitro or in vivo potency of mineralocorticoids, so that it is difficult to evaluate the specificity or relevance of this observation. In any case, it is unlikely that the 100-fold excess of 18-OH-DOC metabolite relative to aldosterone would be achieved in man in whom both steroids are secreted at approximately the same rate. In a recent examination of possible allosteric or cooperative effects of 16α,18-dihydroxy-DOC on aldosterone binding to cytosol mineralocorticoid receptors, no effect was found.[41]

In the experimental model of ACTH-induced hypertension in sheep referred to earlier,[34,35] infusion of the known components of the adrenocortical effluent did not reproduce the hypertension, but when 18-OH-DOC was added at an infusion rate of 100 μg/hour for 5 days there was a significant increase in blood pressure. However, the amount of 18-OH-DOC administered per hour for one sheep equaled the 24 hour secretory rate of the steroid in man.

Secretion of 18-OH-DOC in Experimental Hypertension

There has been considerable interest in implicating 18-OH-DOC in experimental hypertension in the rat. In evaluating these efforts it would be well to recall that the rat is normally subjected to very high levels of this steroid, sometimes even exceeding the level of corticosterone, the major glucocorticoid in that species.[42] In addition, 18-OH-DOC in rat plasma is largely unbound to corticosteroid binding globulin (Varsano-Aharon N and Ulick S, unpublished data) so that the steroid is free to exert whatever biologic effect it is capable of. Thus the normotensive rat, serving as its own bioassay, provides evidence against a hypertensive effect by the relatively large concentrations of 18-OH-DOC to which its tissues are constantly exposed.

Salt-susceptible hypertension: Rapp and Dahl[43] made the interesting observation that when Sprague-Dawley rats were bred for sensitivity and resistance to salt-induced hypertension, two genetic phenotypes were separated, with different 18-OH-DOC/corticosterone secretory ratios. The salt-sensitive animals have the higher ratio, which is also found in spontaneously hypertensive rats and normotensive Wistar rats and must therefore be considered normal. It is the low ratio in the resistant animals that is abnormal. Other genetic loci may account for the increased blood pressure in the salt-sensitive group.[44] In addition, the failure of 18-OH-DOC secretion to suppress in the presence of a large salt intake might tend to augment its hypertensive potency. Although these genetic differences in 18-OH-DOC secretion do not directly establish an etiologic role for the steroid in this form of experimental hypertension, some interesting implications regarding the mechanism of 18-OH-DOC and corticosterone synthesis were revealed, which will be discussed below. Salt-sensitive and resistant rats show other important differences in addition to their adrenal phenotype, and their kidneys differ in renal papillary plasma flow and the ability to secrete antihypertensive factors.[45] Salt-resistant rats show increased amounts of a colloid-like deposit in their pituitary glands.[46]

Spontaneously hypertensive rat: Adrenocortical factors in the spontaneously hypertensive rat[47] were suggested by increased pituitary and adrenal weight in the face of low plasma renin activity and the prevention of hypertension with the removal of these organs. Baer et al.[48] found that adrenalectomy delayed but did not prevent the development of hypertension. Moll et al.[49] found lower adrenal vein concentrations of 18-OH-DOC and other known steroids in spontaneously hypertensive rats than in control rats. Peripheral levels of aldosterone are also decreased[50] if stress-induced pituitary stimulation is avoided. Thus the suppression of the renin-angiotensin aldosterone system in the spontaneously hypertensive rat is not associated with any demonstrable steroid abnormality.

Adrenal regeneration hypertension: In 1955, Skelton[51] noted the development of hypertension in an incompletely adrenalectomized rat in which one adrenal gland had regenerated from a capsular remnant. Since then, hypertension induced by adrenal regeneration has been an actively investigated experimental model. The standard preparation involves unilateral adrenonephrectomy and removal of the medulla from the remaining adrenal gland. When given a solution of 1 percent saline, this sensitized animal becomes hypertensive after 3 to 4 weeks while the adrenal gland regenerates. Secretion of an adrenal hypertensive factor during regeneration is suggested by the prevention of the hypertension by steroid inhibitors or antagonists or by the suppression of pituitary ACTH.[52–54] During the week after enucleation there is marked sodium retention that appears to be pituitary- and adrenal-dependent, although it occurs at a time when the production of known steroids is very low. Gaunt et al.[55,56] have emphasized the strategic importance of this period of sodium retention in relation to the subsequent development of hypertension.

Initial interest in the possible participation of 18-OH-DOC in adrenal regeneration hypertension came from in vitro studies that, although they showed low production of 18-OH-DOC, focused on a somewhat greater than normal response of both 18-OH-DOC and corticosterone to ACTH.[27] It is not clear how this observation would argue for unique participation of 18-OH-DOC in this form of experimental hypertension. The more relevant in vivo measurements[57] did not show increased peripheral levels of 18-OH-DOC at 4 weeks. Grekin et al.[58] found that the initially low 18-OH-DOC and corticosterone secretions did recover to normal or elevated levels by 6 weeks after enucleation, well after hypertension had already been established. Thus there is no evidence for participation of 18-OH-DOC either before or during the development of adrenal regeneration hypertension.

A more likely steroid factor is 11-deoxycorticosterone (DOC), which has the potency to exert a significant biologic effect and is increased early in the regeneration process.[59–61] The mechanism of its increase is apparently a delay in the recovery of the 11β-hydroxylase system relative to that of cholesterol side-chain cleavage.[61] Although DOC levels are increased in adrenal regeneration hypertension, a biologically significant elevation has not been established. Rapp[53] also

reported that rats with adrenal regeneration hypertension, unlike those with DOCA hypertension, were not hypokalemic. Another rather strong argument against the view that excess DOC causes adrenal regeneration hypertension comes from observations by Hall et al.,[62] who found that Long-Evans rats, which are refractory to the development of DOCA-induced hypertension, are nevertheless highly susceptible to adrenal regeneration hypertension.

Despite much work on the steroid pattern of the regenerating adrenal gland in this interesting model, the mechanism of hypertension remains undefined. Nonsteroid mechanisms might also play a role; for example, there is the pressor effect of prolonged stimulation by the renin-angiotensin system itself secondary to the reduction in functional adrenocortical mass during regeneration. Angiotensin II might be a pressor agent under these circumstances despite the hypoadrenal state, particularly in a sensitized animal.

Estimates of Secretion of 18-OH-DOC in Hypertensive Patients

Melby et al.[21] reported that the mean excretion of urinary tetrahydro 18-OH-DOC in 30 patients with low renin hypertension was 38.4 μg/day or approximately twice normal. In a recent expansion of their series to 67 patients,[40] the incidence of elevated excretion of the metabolite was 5 to 10 percent. An examination of their values for urinary tetrahydro-18-OH-DOC reveals a discontinuous or bimodal distribution, suggesting the existence of at least two populations of low renin hypertensive patients, with normal values in one and elevated values in another. Of the 10 patients with elevated values whose clinical features are presented in some detail,[21] 6 proved to have some form of abnormal adrenal histologic feature such as nodular hyperplasia, bilateral hyperplasia or adenoma. This finding suggests that elevated tetrahydro-18-OH-DOC might be more prevalent in a definable subpopulation of the low renin group with abnormal adrenal histologic features but lower in a general unselected low renin hypertensive population and, as such, might have greater significance as an indicator of a subgroup than as an etiologic factor in low renin hypertension.

Nowaczynski et al.[63] report a much higher incidence rate (60 percent) of increased secretion of 18-OH-DOC in hypertensive patients, including those with normal as well as low plasma renin activity. The magnitude of the elevation was also much greater, with mean secretory values of 600 and 1,800 μg/day in patients with normal and low renin hypertension, respectively.[64] Williams et al.[65] measured plasma concentrations of 18-OH-DOC by radioimmunoassay and found no significant difference between patients with low or normal renin hypertension and normal subjects consuming a low salt diet. An interesting feature of their report was a fourfold increase in plasma 18-OH-DOC in response to a low sodium diet, apparently reflecting their ability to detect and measure the small glomerulosa zone contribution of 18-OH-DOC. These authors[65] did find small but apparently significant increases above normal in the plasma levels of 18-OH-DOC in patients with normal renin hypertension but not in the low renin group having large salt intake.

Although the data of Melby and Dale[40] and Williams et al.[65] differ from our data in the incidence or existence of overproduction of 18-OH-DOC in the hypertensive renin subgroups, the magnitude of overproduction claimed was generally only twofold. Their normal plasma concentrations[65,66] are in keeping with our values for the secretory range, assuming the metabolic clearance rate[21] of a steroid that circulates largely unbound to plasma proteins.[63] An explanation of the 6- to 18-fold increases reported by Messerli et al.[64] is not apparent, but it would seem unlikely that all groups are measuring the same substance.

Problems in the chemical estimation of 18-OH-DOC: Although the double isotopic secretory rate method is capable of great precision in that it corrects for variations in metabolism as well as losses in the chemical procedure,[67] its validity rests on the purity of the tracer and the achievement of constant specific activity of the measured metabolite. In addition, the estimation of 18-OH-DOC does present special problems because of a unique chemical property, the tendency first noted by Dominguez[68] to exist in variable amounts of more and less polar chromatographically separable forms. This property has recently been shown to be due to reaction with alcoholic solvents catalyzed by traces of acidic impurities to form ketal derivatives.[69] Thus the two forms of 18-OH-DOC would not be encountered in vivo but are artifactually formed in the course of analysis. If the tracer of 18-OH-DOC were in this ketal form, the double isotopic secretory rate method would tend to overestimate the result. Methods to assure the purity of 18-OH-DOC and its metabolites and to prevent formation of ketal derivatives have been described.[69]

Methods

In vitro studies: Slices of an adenoma from a proved case of Conn's syndrome (aldosteronoma) were incubated with ^{14}C-progesterone over a range of substrate concentration in Krebs Ringer's tris buffer, pH 7.4 along with nicotinamide adenide dinucleotide phosphate (NADPH). Adjacent adrenal cortex, incubated in the same way, served as a control. Steroidal products were analyzed and quantitated by adding ^{3}H-labeled steroids to the incubate extract and purifying chromatographically to a constant ^{3}H/^{14}C ratio.

Secretory and excretory rates: 18-OH-DOC was labeled by catalytic exchange and purified chromatographically as described.[69] The specific activity of the product was 0.9 mCi/μmol. The labeled steroid was stored in alcohol distilled from sodium hydroxide or alcohol containing 0.1 percent triethylamine. The absence of the 20-ketal derivative, the less polar form of 18-OH-DOC, was verified as described.[69] The 3α,5β-tetrahydro derivative of 18-OH-DOC was prepared by a general method of enzymatic reduction.[70]

The 30 patients were studied at the Veterans Administration Hospital except as indicated (see Tables III and IV).

Secretory rates were determined after the injection of 5 μCi of ^{3}H-18-OH-DOC. The 24 hour urine specimen collected after

TABLE II

Chromatographic Purification of Etiolactone Derivative of Tetrahydro 18-OH-DOC

Chromatographic System	Reference Steroid	Mobility Relative to Reference
1. Toluene:methylcyclohexane (5:1)/formamide.	Androstenedione	1.2
Acetylate with ^{14}C-acetic anhydride.		
2. Heptane/formamide to edge.	Progesterone	1.2
3. Repeat 2.		
4. Silica gel thin layer:dichloroethane/methanol (99:1).	Progesterone	1.8
5. Alumina thin layer:toluene.	Progesterone	1.4

All metabolites and derivatives were located for elution by radioactive scanning.

the injection contained at least 70 percent of the radioactivity and was used for isolation of the metabolite. In both procedures direct periodate oxidation of urinary glucuronides to the etiolactones was carried out as described for the tetrahydro metabolites of aldosterone and 18-hydroxycorticosterone.[71,72] The etiolactone of tetrahydro-18-OH-DOC was isolated and purified by the sequence shown in Table II. Constant specific activity was achieved in all determinations according to the described criteria.[72] If the tritium/^{14}C ratios between chromatograms 4 and 5 were greater than 10 percent, then the last two steps were repeated.

Results

Regulation of 18-OH-DOC secretion in normal and hypertensive subjects: Table III compares the secretion of 18-OH-DOC with that of cortisol and the

TABLE III

Response of the Secretion of 18-OH-DOC and Other Corticosteroids to Selective Stimulation and Suppression by ACTH and the Renin-Angiotensin System (21 subjects)*

Case no.	Diagnosis/ Conditions	Corticosteroid Secretory Rates			
		18-OH-DOC (μg)	Aldosterone (μg)	18-OH-B (μg)	Cortisol (mg)
		Normal Subjects			
1a	Control	90	140	340	15.1
1b	Dexamethasone	44	110	250	3.8
2a	Control	105	105	300	13.6
2b	Dexamethasone	35	85	210	2.1
3a	Control	60	91	220	12.2
3b	ACTH	555	206	455	81.5
4a	Control	124	130	350	16.2
4b	ACTH	1436	225	740	145
Normal values		95 ± 24	117 ± 25	260 ± 46	15.1 ± 1.3
		Subjects With Pituitary Disorders			
5	Hypopituitarism	32	105	210	1.9
6	Hypopituitarism	25	75	155	1.4
7	Cushing's syndrome	180	80	210	43.5
		Hyperaldosteronism Secondary to Sodium Depletion or Edema Formation			
8a	Normal Na depleted	120	380	720	...
8b	Normal Na repleted	110	55	155	...
9	Hepatic cirrhosis	96	500	775	...
		Idiopathic Hyperaldosteronism†			
10	...	82	295	870	...
11‡	...	18.5	112	275	...
		Dexamethasone-Suppressible Hyperaldosteronism			
12‡	...	39	64	143	...
		Advanced Hypertension With Secondary Hyperaldosteronism			
13	...	47	409	...	...
14	...	58	208	...	...
15	...	65	335	810	...
16	...	102	363	...	...
		Low Renin Spironolactone-Responsive Hypertension§			
17	...	86	131	...	...
18	...	90	117	...	...
19	...	92	42	...	...
20	...	95	114	...	...
21	...	129	179	...	...

* ACTH gel, 20 units every 6 hours, and dexamethasone, 0.5 mg every 6 hours, were each administered for 2 days, and steroid secretory rates were determined on the second day.

† The diagnosis of idiopathic hyperaldosteronism in Case 10 was confirmed at surgery and in Case 11 it was determined by bilateral adrenal vein catheterization.

‡ The steroid values in Cases 11 and 12 are the excretory rates of the major urinary tetrahydro metabolites. These specimens were kindly made available by Dr. Maria New.

§ Low renin hypertensive patients from the Mount Sinai Hypertension Clinic, New York, N.Y., were kindly made available for study by Drs. Lawrence Krakoff and Milton Mendlowitz. Patients were classified on the basis of plasma renin activity and urinary sodium levels by Krakoff according to Laragh's criteria.

glomerulosa zone steroids aldosterone and 18-hydroxycorticosterone under conditions of selective stimulation of ACTH or the renin-angiotensin system. In response to stimulation or suppression of ACTH, the secretion rates of 18-OH-DOC and cortisol paralleled each other, whereas the changes in aldosterone and 18-hydroxycorticosterone were of much smaller magnitude. In contrast, the selective stimulation of the glomerulosa zone associated with the hyperaldosteronism of sodium depletion, edema formation and the renal involvement of advanced hypertensive disease evoked proportional increases in aldosterone and 18-hydroxycorticosterone but no significant change in 18-OH-DOC. In addition, 18-OH-DOC was not increased in idiopathic- and dexamethasone-suppressible hyperaldosteronism, whereas 18-hydroxycorticosterone and aldosterone were increased proportionately. Small increases in 18-OH-DOC were observed in primary aldosteronism, as described later. In a small series of consecutive patients with low renin spironolactone-responsive essential hypertension, the secretion of 18-OH-DOC was entirely within the normal range.

18-OH-DOC in adrenal biosynthetic defects: The steroid pattern was determined in two adrenal biosynthetic defects to provide some insight into the mechanism of secretion of 18-OH-DOC (Table IV). The production of 18-OH-DOC was greatly increased in the 17α-hydroxylase defect but was virtually undetectable in the 11β-hydroxylase defect. Excessive stimulation by endogenous ACTH in the untreated state was reflected by overproduction of DOC in all patients and increased excretion of the metabolites of either corticosterone or 11-deoxycortisol (compound S). Thus the patients with the 11β-hydroxylase defect differed from the 21 subjects whose data are shown in Table III in that their 18-OH-DOC production did not respond to ACTH. The patient with the 17α-hydroxylase defect showed increased production of 18-OH-DOC and 18-hydroxycorticosterone, both of which were suppressed when dexamethasone was administered.

Steroid Pattern in Primary Aldosteronism

In vitro: Table V presents results of exhaustive analysis of the incubation products of a typical aldosteronoma (Case 2, Table VI). When the products of the tumor were compared with those from the adjacent adrenal cortex as a control, the most striking differences, as expected, were increased formation of aldosterone and 18-hydroxycorticosterone by the tumor. The adenoma also synthesized 1.6 to 1.8 times more of the potential aldosterone precursors 11β-OH-progesterone, DOC and corticosterone than the adjacent adrenal cortex. Although this finding could be ascribed to generally greater biosynthetic activity by the adenoma, it

TABLE IV

Steroid Patterns in Three Cases of Adrenal Biosynthetic Defect

Case no.	Hydroxylase Defect	Urinary Excretion of Tetrahydro Metabolites of (μg/day)				
		Compound B or S	DOC	18-OH-DOC	Aldosterone	18-OH-B
1*	11β-	(THS) 12,200	338	<3	0.9	0.7
2*	11β-	(THS) 9,700	178	<2	1.8	1.9
3a†	17α-	(THB) 15,300	244	1100	<4	590
3b	17α-‡	. . .	14	49	0.46	17.6

*Dr. Jordan Finklestein kindly provided specimens from the brother (Case 1) and sister (Case 2) with the 11β-hydroxylase defect.
†Dr. Edward M. Biglieri kindly provided specimens from his patient (Case 3) with the 17α-hydroxylase defect.
‡ (with dexamethasone).

TABLE V

Steroids Synthesized From Progesterone by Tissue Slices of an Aldosterone-Producing Adenoma Compared with Findings in Adjacent Adrenal Cortex*

Precursor (μg/g tissue)		Products (μg/g tissue)							
Progesterone		11β-OH-Progesterone	DOC	18-OH-DOC	Corticosterone	18-OH-B	Aldosterone	Cortisol	Total† %
Incubated	Unreacted								
Aldosterone-Producing Adenoma									
175	2.3	1.7	3.2	10.4	91.0	19.1	9.3	26.3	94
210	9.1	3.5	23.6	16.0	101	19.5	10.6	32.4	103
350	22.7	10.9	87.5	21.4	138	21.0	12.6	47.2	103
1050	320	39.0	342	41.0	225	28.3	13.6	85.0	104
Adjacent Adrenal Cortex (Control)									
210	30.5	2.0	13.3	4.8	63	0.90	0.061	54.5	80
Adenoma/Control Product Ratio									
210		1.7	1.8	3.3	1.6	21	152	0.60	

* Case 2, Table VI.
† Products plus unreacted progesterone as percent incubated progesterone.

TABLE VI

Steroid Patterns in Primary Aldosteronism

Subjects	Corticosteroid Secretory Rates				
	18-OH-DOC (μg/day)	Aldosterone (μg/day)	18-OH-B (μg/day)	Cortisol (mg/day)	Corticosterone (μg/day)
Patients with primary aldosteronism					
1a	190	1100	2400	15.2	3890
1b	230	...	...	...	...
1c*	105	825	...	5.8	960
1d*	150	...	...	...	...
2	330	495	...	25.1	...
4 normal subjects†	95 ± 22	...	...	15.13 ± 1.27	3850 ± 507
4 normal subjects†	34 ± 6.8	...	...	2.50 ± 0.95	440 ± 45

* Dexamethasone, 2 mg/day, was administered for 2 days, and steroid suppression was determined on the second day.
† Mean values ± standard deviation.

was of interest that the production of 18-OH-DOC by the tumor tissue was even greater or 3.3 times that of the control. Another point of interest was the ability of the aldosteronoma to synthesize appreciable amounts of cortisol. Although the tumor secreted 40 percent less cortisol than the normal adrenal cortex, this amount is much greater than that expected from the normal glomerulosa zone. Thus the steroid pattern in the adenoma differed from the normal glomerulosa zone in that the adenoma synthesized more 18-OH-DOC and cortisol.

In vivo: Efforts to confirm this finding in vivo in the same patient preoperatively are shown in Table VI (Case 2), where significantly increased secretion of both 18-OH-DOC and cortisol were found. Confirmation of this observation and delineation of the component secreted by the tumor was sought in Patient 1. Her secretion of 18-OH-DOC was increased approximately twofold and failed to suppress to expected levels with dexamethasone as it would if it arose from the normal fasciculata zone. Cortisol and corticosterone also failed to suppress normally with dexamethasone, thereby suggesting that this suppression test might be useful in defining the overproduction of these steroids by adenomas.

Aldosteronism due to adenoma versus hyperplasia: In primary aldosteronism due to an adenoma, there was a small but significant increase in the secretion of 18-OH-DOC both in vitro and in vivo. In one patient there was additional evidence for increased secretion of 18-OH-DOC by the tumor in the form of incomplete suppressibility of 18-OH-DOC secretion by dexamethasone. In contrast, two patients with idiopathic hyperaldosteronism due to bilateral hyperplasia (Cases 10 and 11, Table III) secreted normal amounts of 18-OH-DOC. These observations suggest the potential usefulness of measurements of 18-OH-DOC in the differential diagnosis of these two disorders, but studies in more patients are required.

Discussion

Role of 18-OH-DOC in hypertension: Two questions can be raised concerning the role of 18-OH-DOC in both experimental and human hypertension: (1) Is there a significant increase in its secretion rate or plasma level, and (2) if there is such an elevation, can the hypertension be attributed to it? In the case of the three forms of experimental hypertension in the rat, there was no evidence of a relevant increase in the secretion of the steroid. In low renin hypertension in man, there appears to be no reason to doubt the existence of some patients with small but significant increases in the secretion of 18-OH-DOC, but the true incidence in an otherwise unselected low renin hypertensive population is probably much less than previously estimated.[21] We found no examples in a small series of patients with low renin spironolactone-responsive hypertension. In view of the unique methodologic problems in the measurement of 18-OH-DOC, it would be reassuring to see repeated studies in even one patient to document increased 18-OH-DOC secretion or metabolite excretion in order to exclude random measurement error or transient stimulation by endogenous ACTH of a steroid whose pool is not buffered by a large protein-bound reservoir.

In view of the large incidence of adrenal histologic abnormalities in patients with increased production of 18-OH-DOC reported by Melby et al.,[21] as well as our own data indicating subtle differences between the secretory pattern of adenomas and the normal adrenal cortex, it would seem that efforts to confirm and delineate the abnormality in a small number of patients would better advance the problem than single measurement surveys of the incidence of overproduction.

Concerning whether hypertension in either the rat or man can be attributed to 18-OH-DOC even if increased secretion is documented, the data on the biologic activity are clear. At best the activity of 18-OH-DOC as a mineralocorticoid is much less than that of DOC. Even if one assumed that 18-OH-DOC and DOC were equipotent, the reported twofold mean increased excretion[21] could not have any biologic significance because more than a 25-fold increase in the level of 18-OH-DOC would be required to produce a twofold elevation in aldosterone biologic equivalents.

Significance of the Secretion of 18-OH-DOC

Deficient 18-hydroxylation in the 11β-hydroxylase defect: The very low production rates of 18-

OH-DOC in untreated patients with the 11β-hydroxylase defect was surprising in view of the marked stimulation of the steroid normally observed in response to ACTH. This observation that 18-hydroxylation as well as 11β-hydroxylation of DOC was impaired appeared to imply that there were two defects in this hypertensive form of virilizing congenital adrenal hyperplasia. However, to propose two enzymatic defects in an inborn error considered to be the result of a single gene mutation would not be in keeping with the one gene, one enzyme concept.[73] On the basis of these findings in the 11β-hydroxylase defect as well as other data to be summarized later showing a remarkable parallelism between the 18- and 11β-hydroxylation functions of the fasciculata zone, we have suggested that both activities might reside in the same enzyme protein.*

Evidence from the rat adrenal mitochondrial 11β-hydroxylase system: Studies using the rat adrenal fasciculata zone model show that both 11β- and 18-hydroxylase activities are localized in the heavy mitochondria.[74] Both are mixed-function oxidases with common cofactor requirements,[74–78] including the same cytochrome P-450.[79,80] Both activities show similar patterns of stimulation by cyclic adenosine monophosphate (AMP)[81] and calcium[82] and of inhibition by carbon monoxide[74] and metyrapone.[83] All efforts to purify the mitochondrial 11β-hydroxylase have shown proportional retention of 18-hydroxylase activity.[74–78]

In vivo evidence for the parallelism of 11β- and 18-hydroxylases: In the adrenal regeneration that develops after adrenal enucleation in the rat, both corticosterone and 18-OH-DOC decrease in parallel in the early phase and recover together after hypertension develops.[58] Parallelism between corticosterone and 18-OH-DOC is also observed in man (Table IV). When 11β-hydroxylase activity is increased as in the 17α-hydroxylase defect, or after the administration of ACTH to normal persons, 18-OH-DOC is proportionally increased. When 11β-hydroxylation is decreased, as in hypertensive congenital adrenal hyperplasia, 18-OH-DOC is also decreased.

Further evidence for the parallelism of the two hydroxylases comes from the important work of Rapp and Dahl[43,44] on salt-resistant and salt-susceptible hypertensive rats cited earlier. These authors showed that the two enzymic functions are determined by a single genetic locus, but they interpret their data as evidence for the control of a mitochondrial structural protein by a single gene that in turn directs the synthesis of separate 11β- and 18-hydroxylases. The constant steroid ratio within each strain indicates that the relative activities of the two are fixed despite differences in the absolute secretory rate, thus supporting the view of a strong functional if not structural interrelation between the two activities. Rapp and Dahl's evidence also supports the hypothesis of a common enzyme and catalytic site determined by a single gene. In fact, only when a mutation occurred and resulted in an 11β-hydroxylase of presumably different structure, did the 18-OH-DOC/B ratio change. The mutational structural change in the enzyme might occur in its primary structure, but a recent preliminary report[80] suggests that the change resides in the cytochrome P-450 component of the mixed-function oxidase multienzyme system.

The principal objection to the proposal that the fasciculata zone 11β- and 18-hydroxylases might be the same is that the notion appears to be without precedent in mammalian or vertebrate systems. However, the possibility that an enzyme might catalyze hydroxylation at more than one position is suggested by studies of microbial steroid hydroxylases. Lin and Smith[84] in a kinetic analysis of an enzyme of microbial origin capable of hydroxylating three positions on the steroid nucleus have shown that although each hydroxylation reaction has a different velocity, all three had the same Michaelis constant, an unlikely coincidence unless the same enzyme and catalytic site was involved.

In the case of the 11β- and 18-hydroxylases, the major substrate (DOC) is the same, and both positions are on the β-surface of the steroid and spatially close. There could be sufficient flexibility in the region of the catalytic site to accommodate two possible orientations of the substrate so that *either* the 11β *or* 18 position was activated or there could be two conformations of the enzyme. The more probable orientation of substrate and enzyme favors 11β-hydroxylation since this is the more abundant product in all species studied.

If a single hydroxylase activates *either* the 11β *or* the 18 position, how does the doubly hydroxylated derivative 18-hydroxycorticosterone arise? The proposal of the single hydroxylase of diminished specificity was made for the mitochondrial enzyme of the fasciculata zone, which is not the major site of synthesis of 18-hydroxycorticosterone. However, the fasciculata zone does very likely secrete 18-hydroxycorticosterone in the 17α-hydroxylase defect.[22,85] Of the two possible double hydroxylation sequences, 18-hydroxylation of corticosterone would appear to be a more likely mechanism than 11β-hydroxylation of 18-OH-DOC, since the fasciculata zone synthesizes very little 18-hydroxycorticosterone from early precursors[19,86] but can convert corticosterone to 18-hydroxycorticosterone.[87]

The suggestion that the fasciculata zone 18- and 11β-hydroxylases might be the same enzyme is intended as a working hypothesis to explain the significance of the secretion of 18-OH-DOC in man and other species. The hypothesis is amenable to testing and could be (1) disproved by achieving a separation of the two hydroxylase activities, or (2) supported by finding the same Michaelis constant for both hydroxylases in the rat mitochondria as was shown in microbial systems.[84] Rapp and Dahl[43] did evaluate the enzyme kinetics for each hydroxylation but the variability in their double reciprocal plots did not permit a conclusion about whether Michaelis constants for each hydroxylation were the same or significantly different. Whether or not an 11β-hydroxylase can be isolated devoid of 18-hydroxylase activity, there remains a large body of data indicating a functional interrelation and dependence

* Presented at the Searle Sixth Aldosterone Conference, Atlanta, Ga., June 1974.

of the two enzyme activities and of the secretion of the two products, 18-OH-DOC and corticosterone. Another corollary of the hypothesis that is amenable to testing is that the 18-OH-DOC/B secretory ratio should be relatively constant for steroids arising from the normal fasciculata zone. Thus, all circumstances in man in which 18-OH-DOC is elevated should be accompanied by a proportional increase in corticosterone. If the ratio does not remain relatively constant, not only in the same but also among different subjects, one might suspect differences in the 11β-hydroxylase system that might either serve as genetic markers or suggest a cell of origin or histology other than that of the normal fasciculata zone.

Is hypokalemia an obligatory feature of the hypermineralocorticoid state? After the administration of a mineralocorticoid, sodium retention occurs until extracellular and intravascular volume have expanded to a certain critical point, after which the kidney "escapes" from the sodium-retaining effects of the hormone.[88] Increased delivery of sodium to distal tubular sodium/potassium exchange sites and augmented transport under the influence of the hormone leads to enhanced kaluresis and hypokalemia. Although one might expect that this chain of events would lead to proportional and predictable kaliuretic responses to a given dose of mineralocorticoid, the hypokalemic effect may be variable and is sometimes dissociated from the hypertensive effect. Thus, hypokalemia may be slight in mild cases of hyperaldosteronism,[89] particularly if the sodium intake is small. Another example of this dissociation is observed in the 11β-hydroxylase defect of congenital adrenal hyperplasia in the untreated state, in which hypertension is observed regularly whereas hypokalemia, although it does occur, is quite rare.[90] A dissociation between hypertension and hypokalemia in the opposite direction sometimes occurs in the ectopic ACTH syndrome, associated with overproduction of DOC along with other steroids in which hypokalemia may dominate the clinical findings more than the hypertension.

An observation by Edelman[91] suggests how other components of the steroid pattern could modify the intensity of the mineralocorticoid effect. In measurements of sodium transport, 11-deoxycortisol (compound S) was found to be a weak aldosterone agonist but a more effective antagonist. Thus the 11-deoxy steroid, which is secreted in such large amounts in patients with the 11β-hydroxylase defect, is capable of antagonizing and moderating the mineralocorticoid effect of the excessive DOC secreted. Other examples of dissociation between sodium-retaining and kaliuretic effects of mineralocorticoids have been cited.[41] Nevertheless, the weight of evidence favors the view that a mineralocorticoid mechanism that is sufficient to produce hypertension will also lead to potassium depletion. Thus, the normokalemia of the typical patient with low renin hypertension argues against the secretion of a mineralocorticoid factor.

Other possible adrenocortical mechanisms: An ambitious effort involving a search for a sodium-retaining factor in the urine of patients with low renin hypertension has been reported to show increased amounts of biologically active material in such patients.[92] The suggested identity of the active substance as 16β-hydroxydehydroepiandrosterone has not been confirmed (Liddle GW, unpublished data), and others[93,94] have been unable to demonstrate significant mineralocorticoid activity for the steroid. We have not found increased excretion of 16-oxygenated C-19 steroids in patients with low renin hypertension.[95]

There have been reports of hyporeninemic, hypokalemic hypertensive syndromes in which production of the known mineralocorticoids aldosterone and DOC was subnormal.[36,96*] The patient we have had the opportunity to study[37] is a child whose clinical findings resembled those of primary aldosteronism with volume-dependent hypertension and hypokalemic alkalosis but very little secretion of aldosterone and cortisol. A sodium-retaining factor found in her urine has not yet been identified. Although these cases are apparently rare, they appear to represent the pure form of an unknown adrenocorticoid-like mechanism and, as such, might be more appropriate models for the study of such factors in human hypertensive disease.

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Renin and Aldosterone Suppression in the Antihypertensive Action of Clonidine

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In 18 hypertensive patients receiving a constant (100 mEq/day) sodium diet, treatment with clonidine (0.3 mg/day for 5 days) decreased blood pressure in 11 patients with high and normal renin levels and 7 with low renin levels. The high and normal renin group had early and rapid reductions in blood pressure and plasma renin activity. In contrast, the low renin group had a more gradual hypotensive response and only a small absolute decrease in plasma renin. For all patients, pretreatment renin levels were related to the initial decrease in blood pressure but not to the reductions measured after 5 days. Thus, two mechanisms of action of clonidine are possible, one related to acute inhibition of the renin-angiotensin system in patients with high and normal renin levels and another that is independent of renin mechanisms and occurs in all hypertensive patients. In six additional patients with high renin levels induced by prior sodium depletion (10 mEq/day sodium diet), clonidine did not reduce blood pressure or renin, thus indicating that the suppressive action of this agent on renin pressor mechanisms occurs only in patients whose elevated renin levels are intrinsic to hypertension and unrelated to sodium depletion.

Of the 18 patients receiving a normal sodium diet, 13 were classified as responding to treatment (decrease in both systolic and diastolic pressures of at least 10 percent). The five nonresponders had a greater weight gain and higher values for aldosterone excretion. For all patients, there was a significant correlation between decrements in blood pressure and in aldosterone, suggesting that the countervailing effects of fluid accumulation on blood pressure in nonresponding patients resulted from a failure of aldosterone to be suppressed. Changes in aldosterone, in turn, correlated significantly with changes in renin. Thus, the antirenin effect of clonidine enhances its antihypertensive action not only by acutely ablating renin-angiotensin pressor mechanisms, but also by inhibiting aldosterone production and thereby minimizing longer-term reactive volume retention during treatment.

Treatment with clonidine effectively reduces blood pressure in a majority of hypertensive patients.[1–3] The agent acts principally within the central nervous system, where it exhibits a stimulatory effect on alpha adrenergic receptors.[4] This, in turn, leads to reduced activity of the sympathetic nervous system and a decrease in blood pressure.[5]

Clonidine also decreases renal secretion of renin.[6,7] The inhibition of renin release by certain other antihypertensive agents, including beta adrenergic blocking drugs[8,9] and methyldopa,[10] has been held to contribute to the reduction of blood pressure. Thus, it is possible that the antihypertensive effectiveness of clonidine is dependent to some degree upon its suppressive action on renin.

To evaluate the importance of hormonal factors in the action of clonidine in man, we studied the effects of clonidine on plasma renin activity and aldosterone excretion in hospitalized hypertensive patients. The study was carried out in a metabolic ward while the patients were re-

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ceiving a constant intake of sodium and potassium so as to avoid diet-induced alterations in renin and aldosterone mechanisms.

In the sodium-depleted rat treated with diuretic agents, blood pressure is maintained to a significant degree by a compensatory rise in activity of the renin-angiotensin system;[11,12] in these animals, clonidine induces a hypotensive response that is mediated by its renin-reducing action.[13] To determine whether a comparable mechanism exists in hypertensive man subjected to sodium depletion, a further group of patients were treated with clonidine during a period of controlled dietary salt deprivation.

Methods

Patients: Studies were performed in 24 hypertensive subjects, 13 men and 11 women aged 28 to 62 years (mean 44 years), admitted to a metabolic ward. All patients gave informed consent for the study and either had never been treated for hypertension or had discontinued all antihypertensive medication at least 4 weeks before admission. Diagnostic evaluation before the study established that 20 patients had essential hypertension, 3 had renovascular hypertension and 1 had hypertension related to chronic glomerulonephritis. In all cases, medical history, physical examination and laboratory screening had excluded intercurrent heart or liver disease or diabetes mellitus. With the exception of the one patient with chronic glomerulonephritis, whose blood urea nitrogen was slightly increased (25 mg/dl), all patients had normal renal function.

Study protocol: After admission to the metabolic ward, each patient was given a diet containing 100 mEq sodium/day and a constant amount of potassium. After 6 days on this diet, 18 patients were given a 5 day course of clonidine (Catapres®, Boehringer Ingelheim), 0.3 mg/day given in three oral doses of 0.1 mg, while they continued the 100 mEq sodium diet. In the other six patients, sodium intake was reduced from 100 to 10 mEq/day after 6 days. After 6 more days of this low sodium diet, clonidine was administered in the previous manner for 5 days while the low sodium diet was continued.

In each patient, daily values for blood pressure and pulse rate were determined as the average of four readings taken in the seated position at 4 hour intervals during the day. Patients were weighed at a constant time each morning. In the 18 patients who received a 100 mEq/day sodium diet throughout the study, plasma renin activity, measured at noontime in the ambulatory state, and urinary aldosterone excretion were measured during the day before the start of treatment with clonidine (control day), and similarly during the final day of treatment. In nine of these patients, these values were also measured during the 1st day of clonidine treatment. In the six patients subjected to sodium depletion, renin and aldosterone were measured on the last day of the 100 mEq/day sodium diet, on the last day of treatment with the low sodium diet alone, and on the final day of combined treatment with sodium depletion and clonidine.

Techniques: Plasma renin activity[14] and urinary aldosterone excretion[15] were measured by radioimmunoassay. Metabolic balance procedures and routine electrolyte determinations were performed as described previously.[16]

To facilitate analysis, each patient was classified into a high, normal or low renin category according to a nomogram relating renin values to concurrent daily sodium excretion.[17] Because only three patients were in the high renin category, their data were included with those of the normal renin group. The Wilcoxon test for paired differences was used for statistical analysis within groups of patients, and the Wilcoxon test for nonpaired data for comparisons between groups. Regression analysis was performed by the Spearman method. Data are given as mean ± standard error of the mean.

Results

Patients Receiving a Constant Sodium Diet

Of the 18 patients who received a constant 100 mEq/day sodium diet throughout the study, 11 were classified in the high and normal renin group (average age 40 years) and 7 in the low renin group (average age 46 years).

Blood pressure: The effects of clonidine, 0.3 mg/day, in the two renin groups are summarized in Table I. By the end of the 5 day treatment period, systolic and diastolic blood pressures were significantly reduced in each group. However, although the ultimate effectiveness of clonidine in reducing blood pressure did not differ significantly in the two groups, the rate of reduction did differ (Fig. 1). Thus, during the 1st day of treatment, the decrease in diastolic pressure of 14 ± 2 mm Hg ($P < 0.01$) in the high and normal renin group was significantly greater ($P < 0.025$) than the reduction

TABLE I

Values Immediately Before and During Treatment With Clonidine (0.3 mg daily for 5 days) (mean ± standard error of the mean)

	Blood Pressure (mm Hg)		Pulse Rate (per min)	Body Weight (kg)	Plasma Renin Activity (ng/ml per hour)	Urinary Aldosterone (μg/24 hours)
	Systolic	Diastolic				
	High and Normal Renin Group (no. = 11)					
Before	183 ± 11	117 ± 7	78 ± 4	69.9 ± 4.1	7.9 ± 2.3	21.3 ± 2.9
After	139 ± 10‡	91 ± 4‡	68 ± 3†	70.3 ± 4.1	3.0 ± 0.9‡	13.0 ± 2.1†
	Low Renin Group (no. = 7)					
Before	169 ± 11	111 ± 6	76 ± 3	74.0 ± 6.3	0.8 ± 0.2	16.7 ± 3.5
After	146 ± 9‡	93 ± 6†	68 ± 3*	74.5 ± 6.2	0.5 ± 0.1	10.6 ± 2.7*

*$P < 0.05$, †$P < 0.025$, ‡$P < 0.01$ when compared with control value.

in the low renin group (3 ± 2 mm Hg). Similarly, the initial decrease in systolic pressure was greater (P <0.05) in the high and normal renin group (25 ± 15 mm Hg) than in the low renin group (7 ± 3 mm Hg). In the succeeding days of treatment there was no significant difference between the additional reductions in blood pressure in the two groups.

During the treatment period, pulse rate was significantly reduced in both groups, decreasing by 10 beats/min (P <0.025) in the high and normal renin group and by 8 beats/min (P <0.05) in the low renin group.

Sodium and potassium: There were no significant changes in either group in mean body weight or plasma concentration of sodium or potassium. There was also no difference between the two renin subgroups in the cumulative retention (sum of the differences between daily dietary intake and urinary output) of sodium and potassium during the treatment period (average values 125 and 97 mEq in the high and normal renin group and 125 and 107 mEq in the low renin group).

Plasma renin activity: There was a 61 percent decrease in plasma renin activity in the high and normal renin group during the study (P <0.01). This change occurred promptly. In the six patients whose measurements were obtained after 1 day of treatment, mean plasma renin activity had decreased from 7.3 to 3.3 ng/ml per hour by 24 hours (P <0.01); but it did not change significantly thereafter and was 2.9 ng/ml per hour at the end of the study. In contrast, pretreatment plasma renin activity in the low renin group was decreased but not significantly changed by the administration of clonidine. Renin and blood pressure values in two representative patients, one with a high renin level and one with a low level are shown in Figure 2.

In contrast to the renin findings, the control urinary aldosterone values in the two groups were not significantly different from each other (P >0.1), and decreased to a similar extent during treatment with clonidine. Thus, mean urinary aldosterone excretion decreased from 21 ± 3 to 13 ± 2 μg/day (P <0.01) in the high and normal renin group, and from 17 ± 4 to 11 ± 3 μg/day (P <0.05) in the low renin group.

Correlation of blood pressure, plasma renin activity and aldosterone excretion: For the patients as a whole, there was a significant correlation between pretreatment values of plasma renin activity and the percent reduction in diastolic blood pressure on the 1st day of treatment (r = 0.66, P <0.01). However, there was no significant correlation (r = 0.13) between these renin values and the reductions in blood pressure measured at the end of the study. Analysis of all 27 renin values measured during the 5 day treatment period in the 18 patients studied gave a significant correlation between percent changes in plasma renin activity and in diastolic blood pressure (r = 0.52, P <0.01). The correlations between changes in plasma renin activity and either cumulative sodium (r = 0.27) or potassium (r = 0.18) retention were not significant.

As with renin, there was a significant correlation between percent changes in aldosterone excretion and in

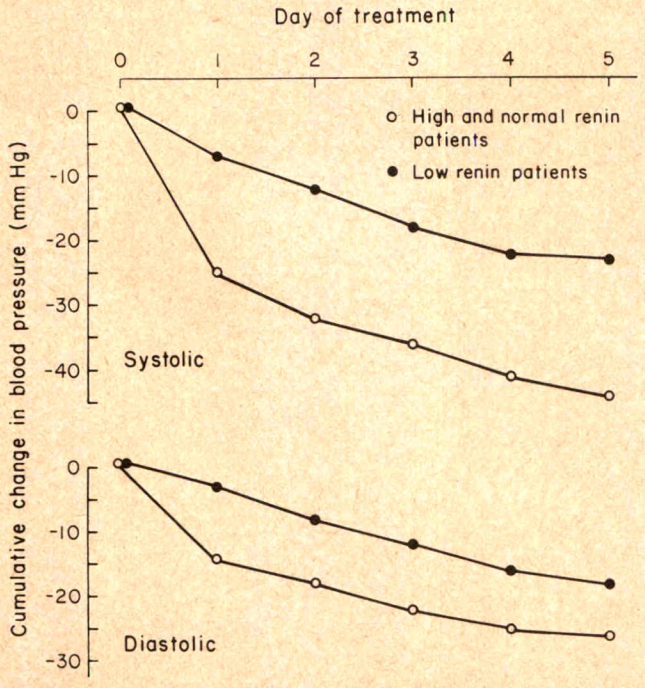


FIGURE 1. Changes in blood pressure in 11 patients with a high or normal renin level and in 7 patients with a low renin level during 5 days of treatment with clonidine, 0.3 mg/day.

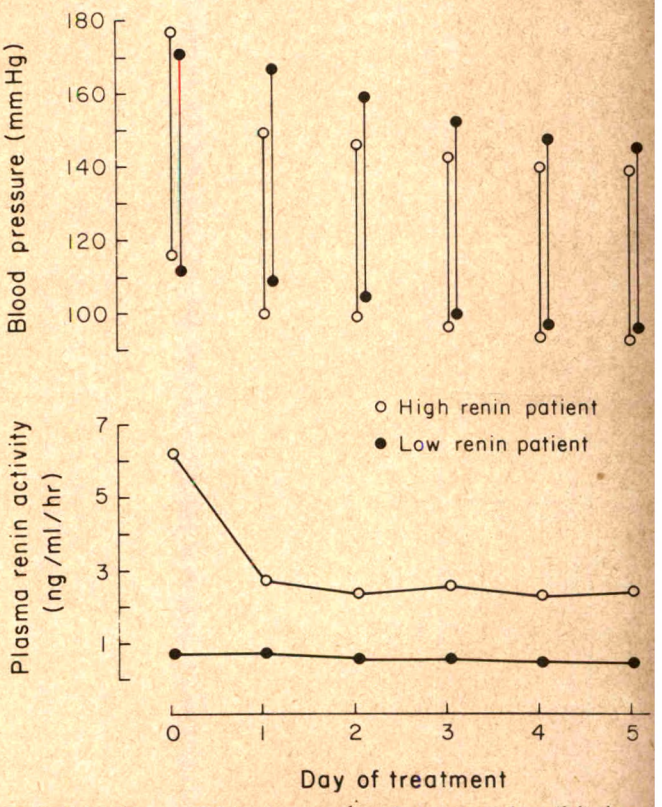


FIGURE 2. Changes in blood pressure and plasma renin activity in a patient with high renin hypertension (open circles) and a patient with low renin hypertension (closed circles) during 5 days of treatment with clonidine, 0.3 mg/day.

diastolic blood pressure ($r = 0.48$, $P < 0.05$) during treatment. Regression analysis further indicated that the changes in aldosterone excretion were associated with changes in plasma renin activity ($r = 0.51$, $P < 0.01$) but were not related to changes in sodium ($r = -0.11$) or potassium ($r = -0.22$) plasma concentrations, the net calculated retention of sodium ($r = -0.07$) or potassium ($r = -0.27$) or body weight ($r = -0.12$).

Responders versus nonresponders: In this study, a satisfactory blood pressure response to clonidine was defined as a reduction in both systolic and diastolic pressures of at least 10 percent. Accordingly, 8 of the 11 patients in the high and normal renin group and 5 of the 7 in the low renin group were considered responders. A comparison between these 13 responders and the 5 patients classified as nonresponders is given in Table II. Apart from the blood pressure response, the principal differences between the two groups were in the treatment-induced changes in plasma renin activity, urinary aldosterone and body weight. Thus, the mean change in plasma renin activity in the clonidine responders (−54 percent) was significantly different ($P < 0.025$) from that in the nonresponders (+7 percent). Similarly, aldosterone excretion decreased more ($P < 0.05$) in the responders (44 percent reduction) than in the nonresponders (12 percent reduction). Mean body weight increased to a greater extent ($P < 0.05$) in the nonresponders than in the responders. Net sodium retention was also somewhat greater in the nonresponders than in the responders during treatment ($P < 0.1$). Changes in pulse rate were the same in the both groups.

Sodium Depletion Studies

Table III summarizes results obtained in six additional patients subjected to sodium depletion and clonidine treatment, (one classified as having a high renin level and three a normal and two a low renin level). In these patients, urinary sodium excretion, which decreased from 103 ± 9 to 11 ± 4 mEq/day ($P < 0.01$) when dietary sodium intake was reduced from 100 to 10 mEq/day, was not further altered when clonidine was superimposed. Similarly, mean body weight decreased during the first phase of sodium depletion ($P < 0.025$) but did not change with clonidine treatment.

With sodium depletion alone, there were small but insignificant reductions in blood pressure. However, clonidine caused both systolic and diastolic pressures to decrease significantly ($P < 0.025$ for both). Unlike patients with high and normal renin levels receiving a constant diet containing sodium, those with sodium depletion alone had no significant changes in blood pressure during the 1st day of clonidine treatment

TABLE II

Effects of Clonidine in Hypertensive Responders and Nonresponders to Clonidine (mean ± standard error of the mean)*

Change in Blood Pressure (mm Hg)		Change in Pulse Rate (per min)	Change in Body Weight (kg)	Change in Plasma Renin Activity (%)	Change in Aldosterone Excretion (%)	Cumulative Sodium Retention (mEq)
Systolic	Diastolic					
Responders (no. = 13)						
−40 ± 6	−30 ± 4	−9 ± 2	+0.3 ± 0.4	−54 ± 15	−44 ± 8	102 ± 20
Nonresponders (no. = 5)						
−11 ± 7‡	− 5 ± 2‡	−7 ± 2	+1.0 ± 0.3*	+7 ± 20	−12 ± 14†	122 ± 15

*Responders had reductions of 10 percent or more in both diastolic and systolic blood pressure: nonresponders had reductions of less than 10 percent in systolic or diastolic pressure, or both, after 5 days of treatment with clonidine (0.3 mg/day).
†$P < 0.05$; ‡$P < 0.01$ when compared with value in responders.

TABLE III

Data in Six Hypertensive Patients with Sodium Depletion and Treatment With Clonidine (mean ± standard error of the mean)*

	Blood Pressure (mm Hg)		Pulse Rate (per min)	Body Weight (kg)	Plasma Renin Activity (ng/ml per hour)	Urinary Aldosterone (μg/24 hours)	Plasma Sodium (mEq/liter)	Plasma Potassium (mEq/liter)
	Systolic	Diastolic						
I. Control	156 ± 7	100 ± 3	76 ± 5	65.9 ± 4.4‡	2.3 ± 0.6‡	32.8 ± 16.3†	135.7 ± 0.8	3.9 ± 0.1
II. Sodium depletion	144 ± 6	96 ± 2	78 ± 4	64.7 ± 4.4	6.5 ± 2.2	52.4 ± 14.4	134.5 ± 2.0	3.9 ± 0.1
III. Sodium depletion plus clonidine	123 ± 6‡	82 ± 5‡	71 ± 3†	64.7 ± 4.5	5.7 ± 1.9	46.7 ± 12.6	131.8 ± 1.8	3.9 ± 0.1

*I = control period of 100 mEq/day sodium diet; II = after 10 days of sodium depletion (10 mEq/day sodium diet); III = after 5 more days of sodium depletion plus treatment with clonidine (0.3 mg/day).
†$P < 0.05$, ‡$P < 0.025$, when compared with value obtained during period II (sodium depletion alone).

(systolic −8 mm Hg, diastolic −3 mm Hg). However, pulse rate in the patients with sodium depletion decreased by an average of 7 beats/min ($P < 0.05$).

Plasma renin activity, which increased threefold during sodium depletion alone ($P < 0.025$), decreased by a mean of only 8.3 percent when clonidine was given. This change was significantly less ($P < 0.025$) than that observed in the 18 patients who received the 100 mEq/day sodium diet throughout the treatment period. Thus, patients in the high and normal renin group with prior sodium depletion resembled patients in the low renin group both in failure to show decreases in plasma renin activity and in pattern of blood pressure response. Urinary aldosterone excretion, which increased during the period of sodium depletion alone ($P < 0.05$), also did not change significantly when clonidine treatment was added. Plasma concentrations of sodium and potassium did not vary significantly.

Discussion

These studies show that clonidine as a single agent provides effective antihypertensive treatment in the hospitalized patient. Thus, 17 of 24 patients (71 percent) receiving either a normal or a reduced sodium diet responded to clonidine (0.3 mg/day) with reductions of at least 10 percent in both systolic and diastolic blood pressures.

Renin-suppressive action of clonidine: Although clonidine significantly reduced blood pressure in patients with high and normal renin levels as well as a low level of renin, the rate of reduction in the two groups was not the same. Whereas blood pressure decreased evenly during the treatment period in the low renin group, the reduction was significantly more rapid in the high and normal renin group, half of the total decrease occurring within the 1st day of treatment. This rapid reduction was probably related to a reduction in vasoconstrictor mechanisms rather than to an effect on volume factors because the changes in body weight and electrolyte balance that occurred in the high and normal renin group were closely similar to those in the low renin group. It is likely that this rapid inhibition of vasopressor mechanisms, which characterized the difference in blood pressure response between the two groups, was dependent upon the suppressive effect of clonidine on renin release. Thus, although plasma renin decreased to less than 50 percent of its control value within the 1st day of treatment in the high and normal renin group, it did not change appreciably in the low renin group. Moreover, for the patients as a whole there was a significant correlation between pretreatment renin values and blood pressure decrements on the 1st day of treatment, although there was no relation between these renin values and the reductions in blood pressure measured at the end of the study. Hence, the acute antirenin effect of clonidine constitutes an important component of its antihypertensive action. Renin-suppressive mechanisms also have previously been shown to play a part in the actions of other antihypertensive compounds, including beta adrenergic blocking agents[8,9] and methyldopa.[10]

Mechanism of clonidine's antihypertensive action: The temporal difference between the two renin groups in their patterns of blood pressure response, together with the difference in their renin responses, appears to confirm a dual mode of action of clonidine: a rapid reduction of blood pressure in patients with high and normal renin levels, related to an acute inhibition of renin-angiotensin pressor mechanisms, and a more gradual antihypertensive effect that occurs in all hypertensive patients regardless of renin status. This latter mechanism may be associated with the reduction in sympathetic activity known to be produced by clonidine,[5] because heart rate decreased uniformly in all hypertensive subjects studied.

In patients whose blood pressure failed to respond to clonidine (nonresponders) weight gain was significantly greater than in responders. There was no difference between these two groups in the degree of bradycardia induced by clonidine, thus further suggesting that the absence of a reduction in blood pressure in nonresponders was due primarily to volume retention rather than to a failure of clonidine to exhibit its antisympathetic effect. In turn, this volume retention appears to have been related to the lack of a decrease in aldosterone production in these patients, for the reduction in aldosterone excretion in the nonresponders was significantly less than that in the responders. The further observation in this study that there was a positive correlation between falls in aldosterone excretion and falls in blood pressure underlines the importance of aldosterone inhibition in the antihypertensive action of clonidine.

Clonidine and aldosterone secretion: There is no known mechanism by which clonidine directly suppresses aldosterone secretion. However, the renin-angiotensin system is known to play a major role in the control of aldosterone,[18] and it is likely that the reductions in aldosterone excretion that occurred in this study resulted from clonidine-induced inhibition of renin release. Thus, in parallel with aldosterone, plasma renin activity decreased significantly in patients classified as blood pressure responders, but failed to change in nonresponders. Moreover, in the patients as a whole, there was a significant correlation between the changes in aldosterone excretion and plasma renin during the study period. The other major factors that can influence aldosterone secretion, alterations in sodium[19,20] and potassium[21,22] balance, were not found to do so in this study.

From these findings a second mechanism by which suppression of renin contributes to the antihypertensive action of clonidine can be postulated: namely, that inhibition of the renin-angiotensin system by clonidine leads to a reduction in aldosterone secretion, thereby preventing the fluid retention that would otherwise reduce or abolish the decrease in blood pressure. The importance of renin suppression in this context was supported in this study by the additional finding of a significant correlation between the induced decrements in plasma renin activity and blood pressure during treatment. This critical antirenin action of clonidine

occurred in all patients studied, including those with low renin levels. Thus, although the decrements in plasma renin caused by clonidine in the low renin group were small, the relative (percent) changes were sufficiently large to produce substantial reductions in aldosterone and thereby to diminish the participation of volume factors in the maintenance of the high blood pressure state.

Effects of sodium depletion on antirenin action of clonidine: In the patients subjected to sodium depletion before and during treatment, clonidine decreased blood pressure but produced only slight reductions in plasma renin activity and aldosterone excretion. Although pretreatment renin levels in these patients did not differ from levels in the high and normal renin group receiving a normal sodium diet, plasma renin activity decreased to a much greater degree in the latter group (60 percent) than in the former (8 percent). Thus, clonidine was far more effective in inhibiting renin release in hypertensive subjects whose renin levels were inherently high than in those whose renin levels were high as a result of sodium depletion.

Clonidine inhibits renin secretion through its action in the central nervous system,[23] abolishing the component of renin secretion dependent upon neural governance. Clonidine may also affect renin by directly stimulating alpha adrenergic receptors within the kidney.[24] However, neither the sympathetic nervous system nor intrarenal alpha receptors appear to be substantially involved in the renin response to sodium depletion. Despite administration of clonidine in sufficiently large doses to produce significant reductions in heart rate and blood pressure, we found no change in plasma renin activity in the patients who were subjected to salt deprivation.

These results are in apparent conflict with data from recent studies in the sodium-depleted rat in which the hypertensive action of clonidine was found to be dependent upon its renin-lowering properties.[13] However, in the rat studies sodium depletion was achieved with the use of furosemide, and it is thus likely that renin levels were being sustained, at least in part, by mechanisms other than those involved in the renin response to sodium depletion induced by dietary salt deprivation.[25]

During the 5 day treatment period, clonidine produced significant reductions in both systolic and diastolic blood pressures in our sodium-depleted patients. Consistent with the absence of a decrease in plasma renin activity in these subjects was the absence of the rapid phase of the hypotensive response found in patients in the high and normal renin group receiving a normal sodium diet. Although aldosterone excretion did not decrease in these patients, the continued rigorous salt deprivation prevented reduction in the antihypertensive response that might otherwise have been caused by fluid retention as in the group eating more sodium.

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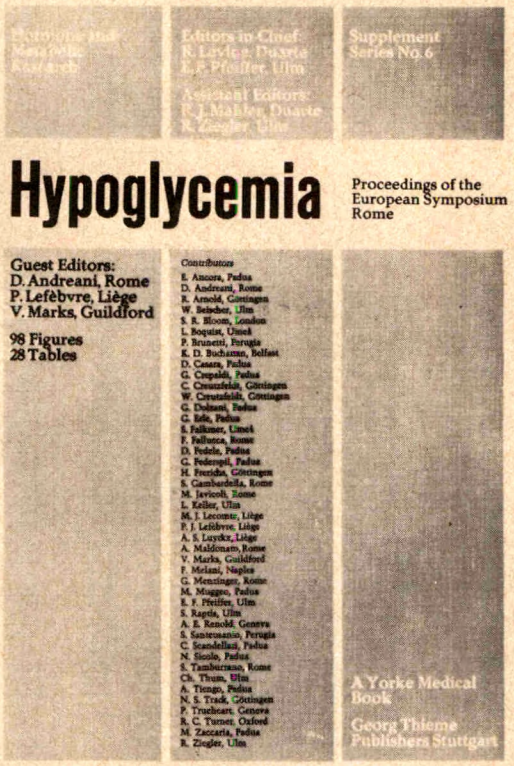
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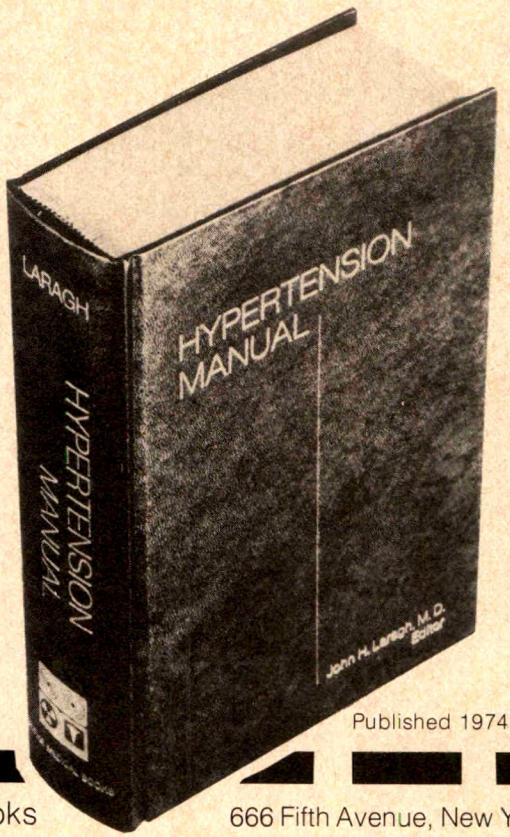
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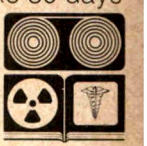
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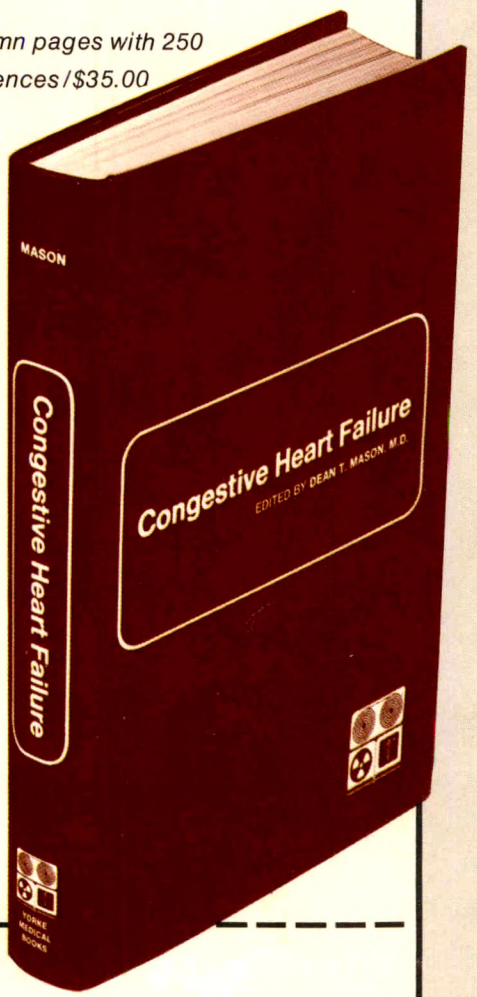
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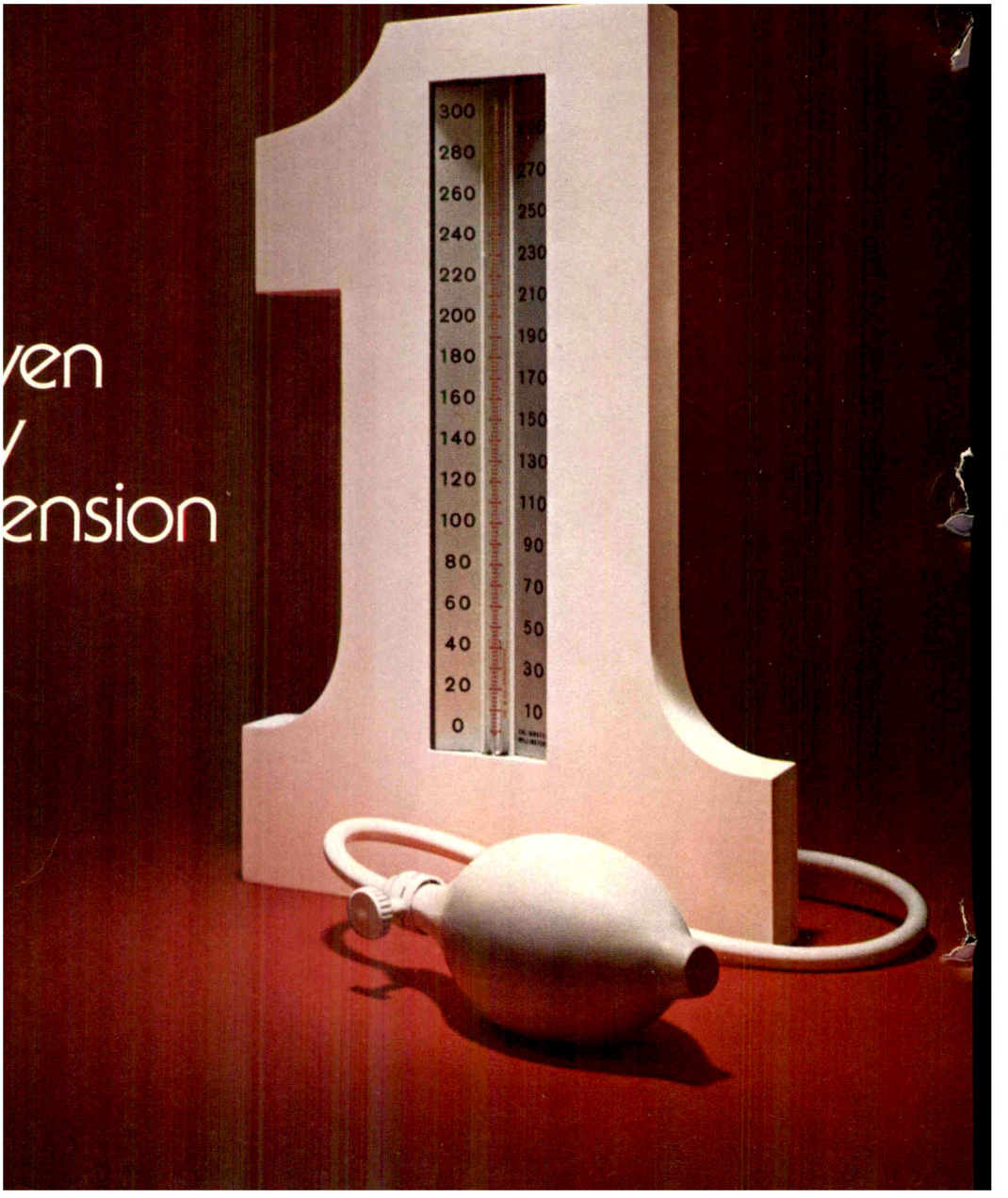
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efficacy

Of those hypertensive patients who may be controlled by HydroDIURIL, as little as 50 mg daily may be adequate for some. In others, 100 mg a day may be required for satisfactory blood pressure control. A few patients may require 200 mg daily in divided doses.

convenience

Single daily doses may represent a useful prescribing option, and the availability of HydroDIURIL in 50- and 100-mg tablet strengths makes the option even more useful. Once-daily therapy often represents greater convenience and fosters better compliance. (See Addendum at right for more dosage details.)

certain therapeutic limitations

Contraindicated in anuria and hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease. For more details, please see the brief summary of prescribing information.

TABLETS: 25 mg, 50 mg, and 100 mg

HydroDIURIL®

(Hydrochlorothiazide | MSD)

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

addendum

MSD
MERCK SHARP & DOHME

Recommended Dosage of HydroDIURIL (Hydrochlorothiazide, MSD) in Hypertension

Starting Dosage
The usual adult starting dose is 50 mg or 100 mg as a single or divided dose. For many patients, the 50- or 100-mg tablets allow once-daily administration for convenience.

Adjusting Dosage
Dosage is increased or decreased according to the blood pressure response of the patient.

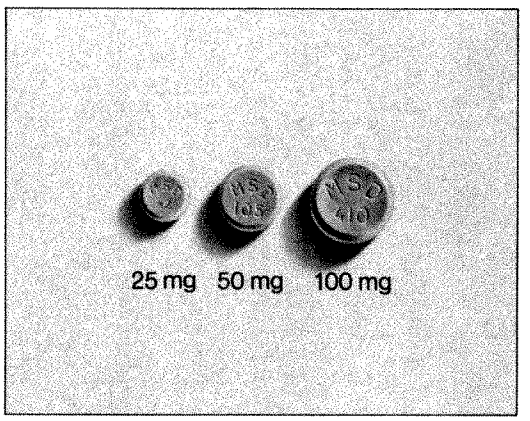
Maximum Dosage
Some patients may require up to 200 mg daily in divided doses. These patients may also benefit from the convenience of the 100-mg tablet.

Use with Other Antihypertensive Agents
HydroDIURIL often enhances the effect of other antihypertensive agents. Careful observation for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

In hypertension

HydroDIURIL®

(Hydrochlorothiazide | MSD)



Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs.

Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

Use in Pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

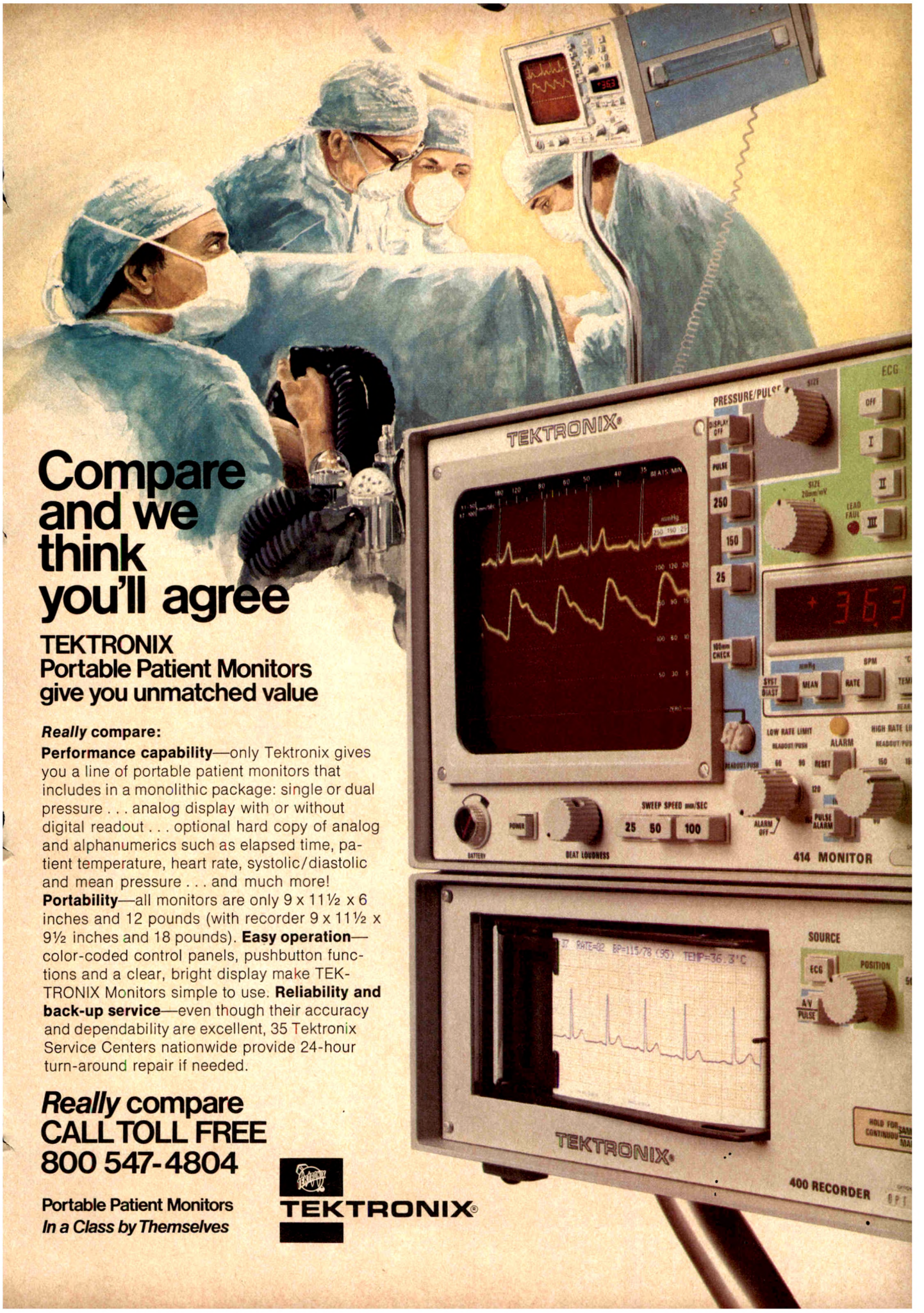
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 25 mg hydrochlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 50 mg hydrochlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Tablets containing 100 mg hydrochlorothiazide each in bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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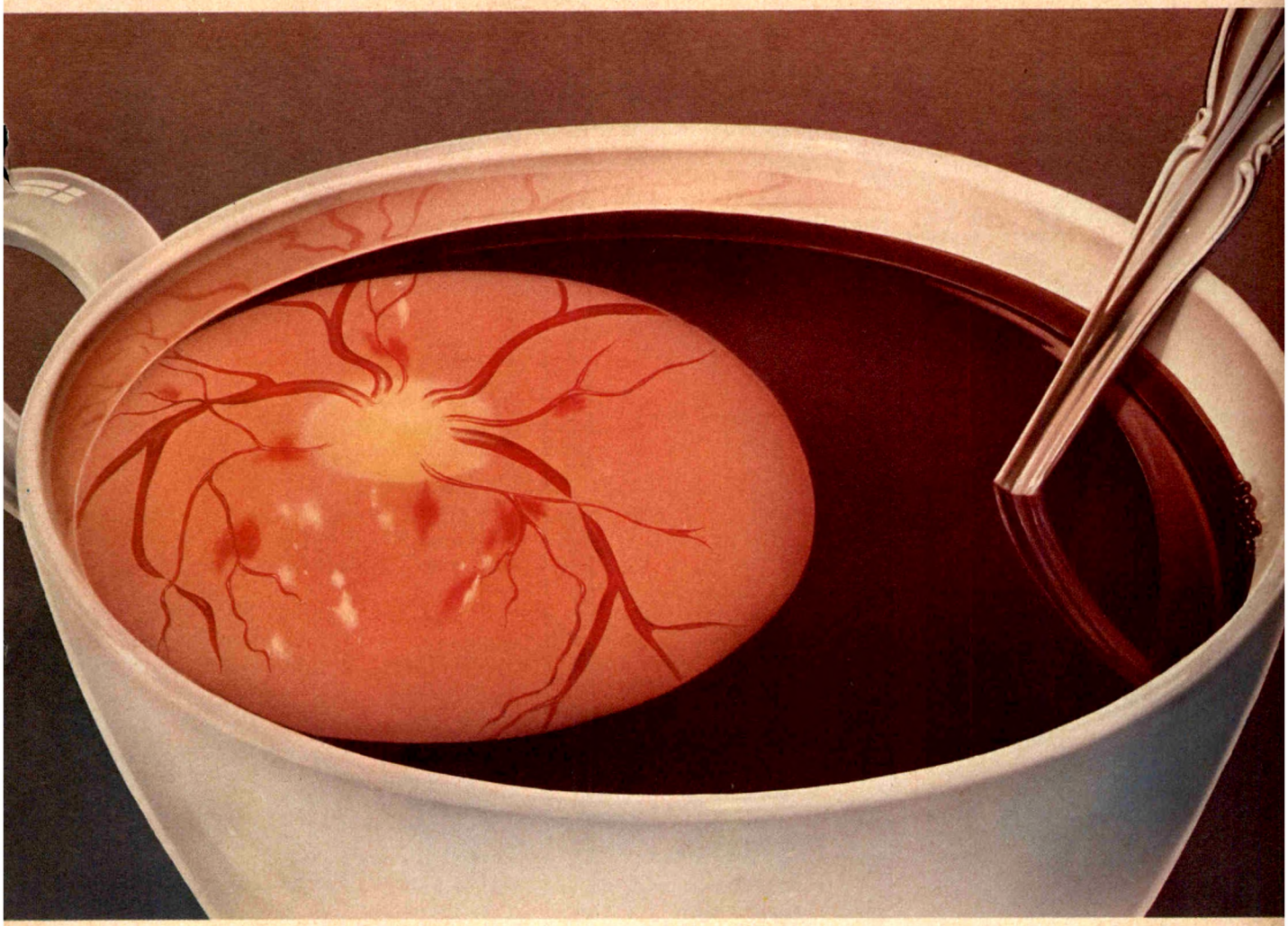
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Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered; especially during the first weeks of therapy.

Signs of idiosyncrasy include febrile reactions, skin eruptions, thrombocytopenic purpura, and respiratory embarrassment. Extreme caution should be exercised in using the drug in patients with severe heart disease and congestive heart failure, with digitalis intoxication, or renal insufficiency. It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

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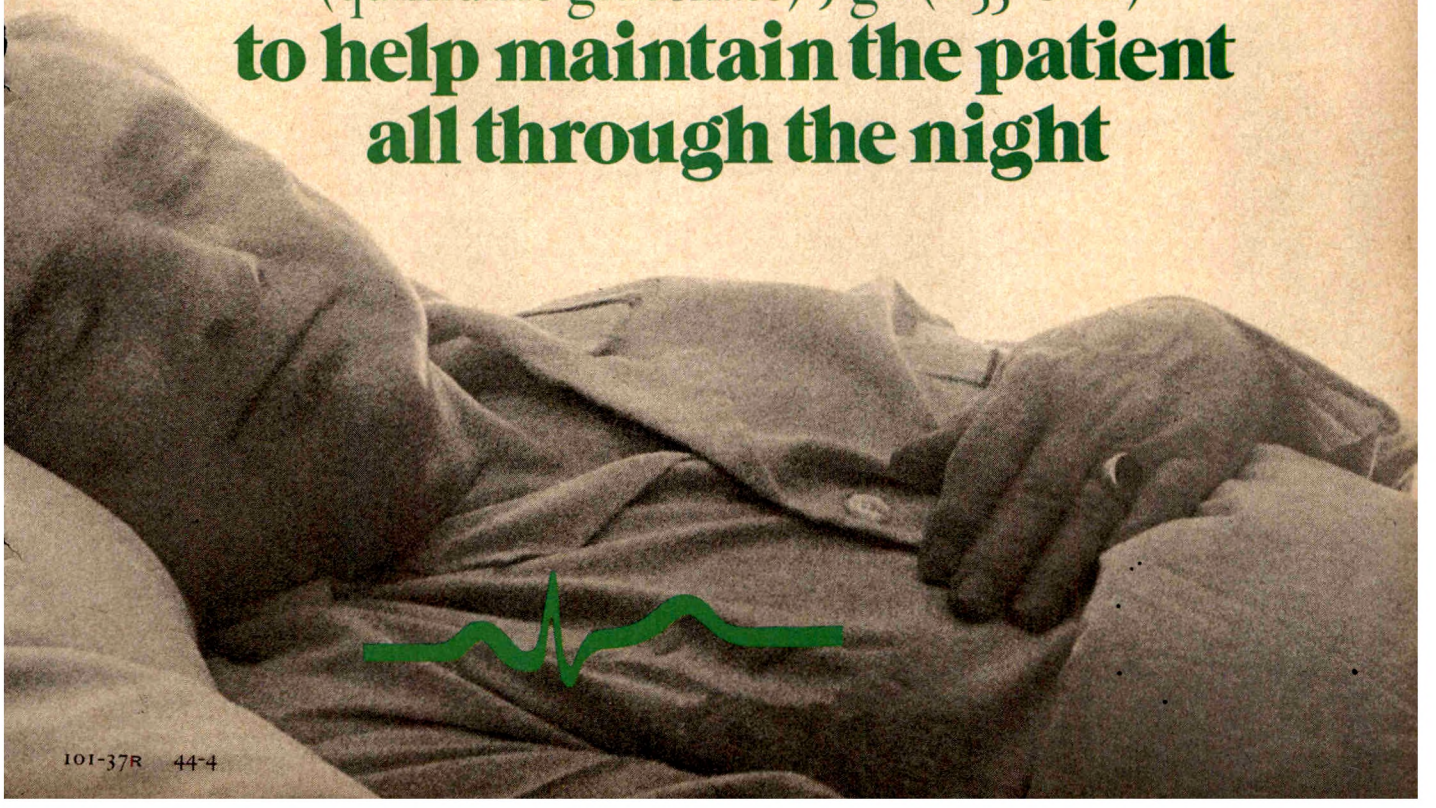
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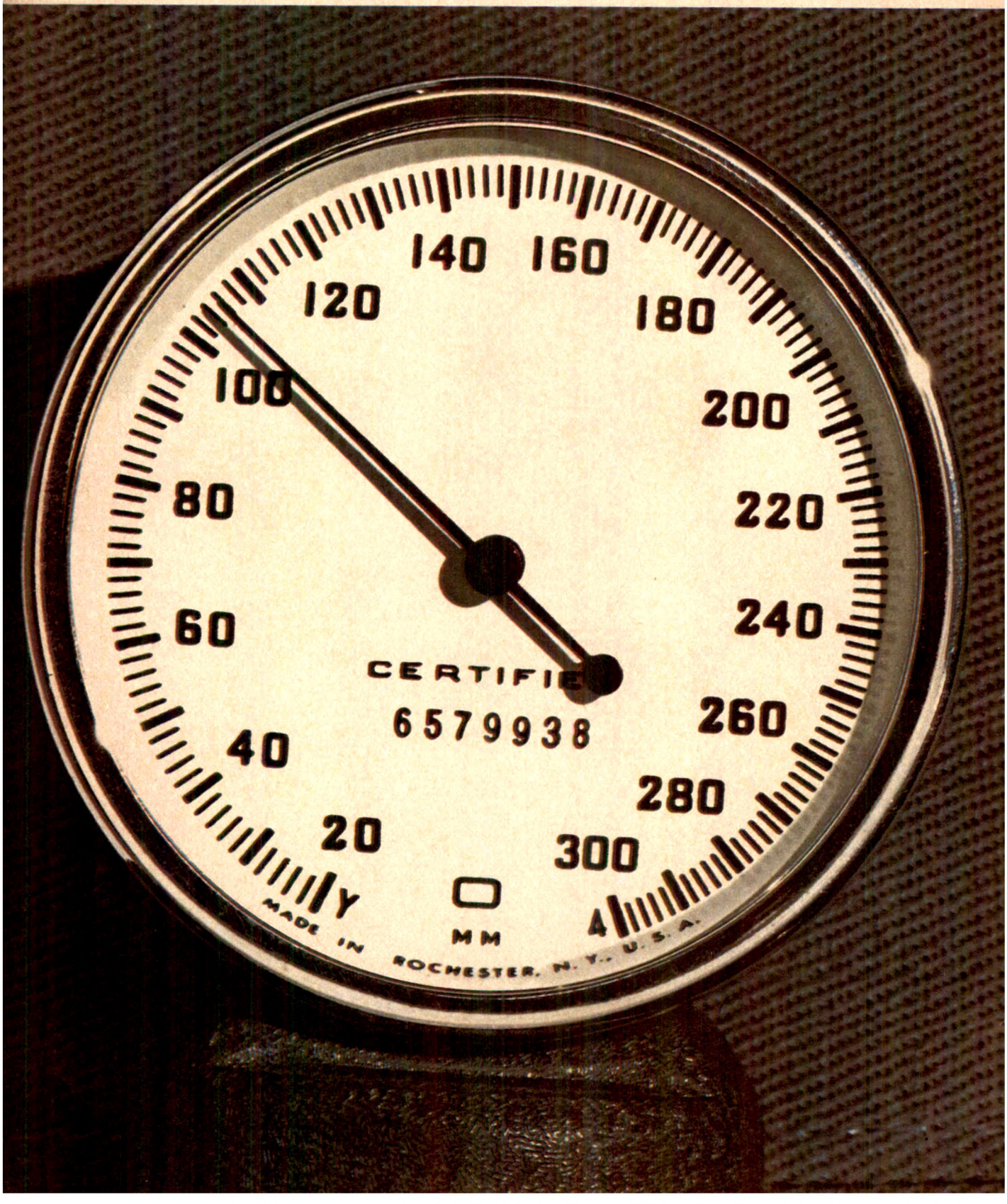
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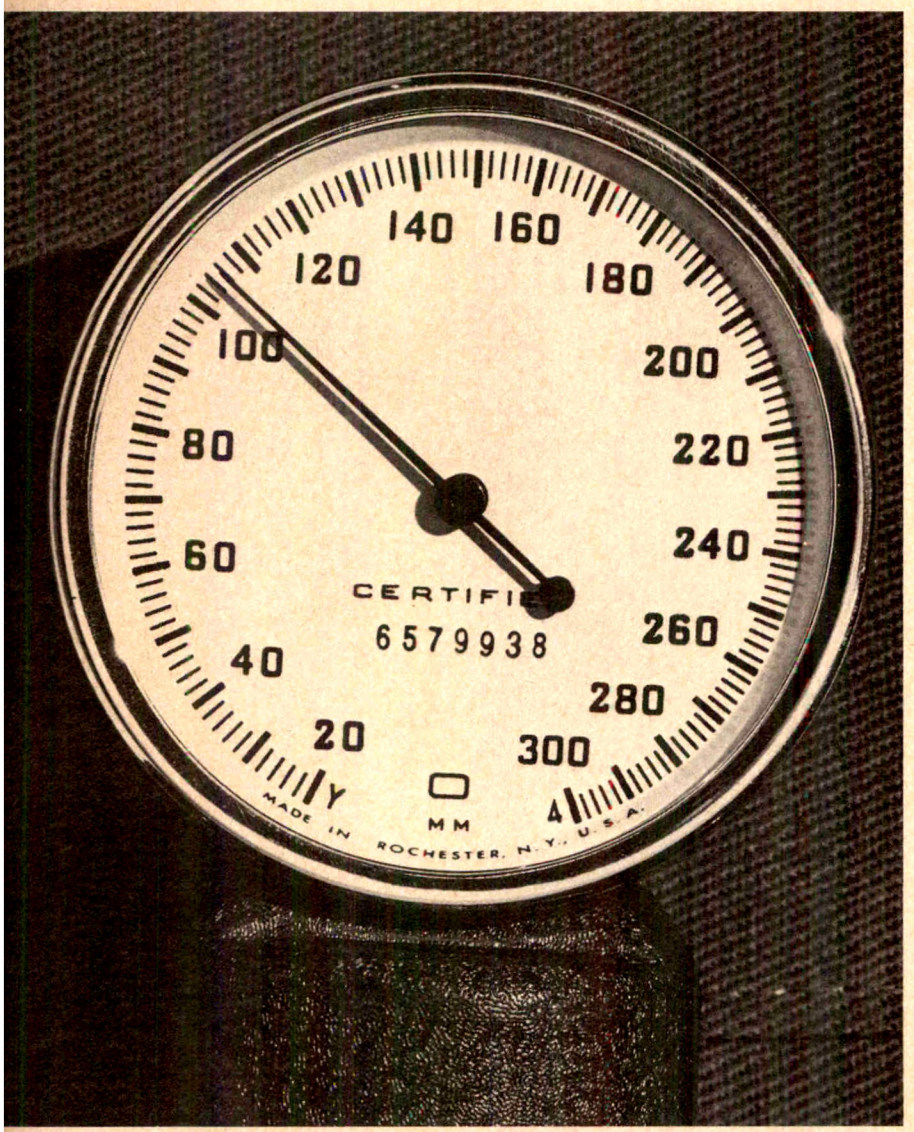
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*

WARNING
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the fixed combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium-sparing action of its 'Dyrenium' component is warranted.

Contraindications: Further use in progressive renal or hepatic dysfunction; hyperkalemia. Preexisting elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs. Routine use of diuretics in otherwise healthy pregnancy.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in severely ill patients with urine volume less than one liter/day, the elderly or diabetics, with suspected or confirmed renal insufficiency. Periodic determinations of serum K^+ should be made. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **The presence of a widened QRS complex or arrhythmia in association with hyperkalemia requires prompt additional therapy.** Thiazides are reported to cross the placental barrier and appear in breast milk; fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and other adverse reactions that have occurred in the adult may result. When used in pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics, or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium® (triamterene, SK&F Co.), and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Do periodic blood studies in cirrhotics to check for nondrug-related variations in blood pictures, and in patients with folic acid depletion, since 'Dyrenium' may contribute to appearance of megaloblastosis. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

DECEMBER 1976

The American Journal of CARDIOLOGY®

VOLUME 38

NUMBER 7

CONTENTS

CLINICAL STUDIES

831 Left Ventricular Performance in Mitral Regurgitation Assessed With Systolic Time Intervals and Echocardiography

KENNETH L. WANDERMAN, MARK J. GOLDBERG, RICHARD S. STACK and ARNOLD M. WEISSLER

A prolonged preejection period (PEP), shortened left ventricular ejection time (LVET) and an increased PEP/LVET ratio characterized the 22 patients with isolated mitral regurgitation of various origins. An increased PEP/LVET ratio greater than 0.50 was consistently associated with echocardiographic evidence of abnormal left ventricular performance; a normal ratio reflected normal or supernormal left ventricular performance. Such use of combined echocardiographic and systolic time interval measurements enhances the analysis of ventricular performance in mitral regurgitation.

836 Echocardiographic and Clinical Spectrum of Mitral Anular Calcification

GEORGE E. GABOR, BRIAN D. MOHR, PREM C. GOEL and BARUCH COHEN

Although the echocardiogram can be used reliably to diagnose calcification of the mitral anulus, care must be taken to distinguish this echocardiographic pattern from that of pericardial effusion and mitral stenosis in particular. Anular calcification may extend into the posterior left ventricular wall, mitral valve leaflets, aortic valve and interventricular septum.

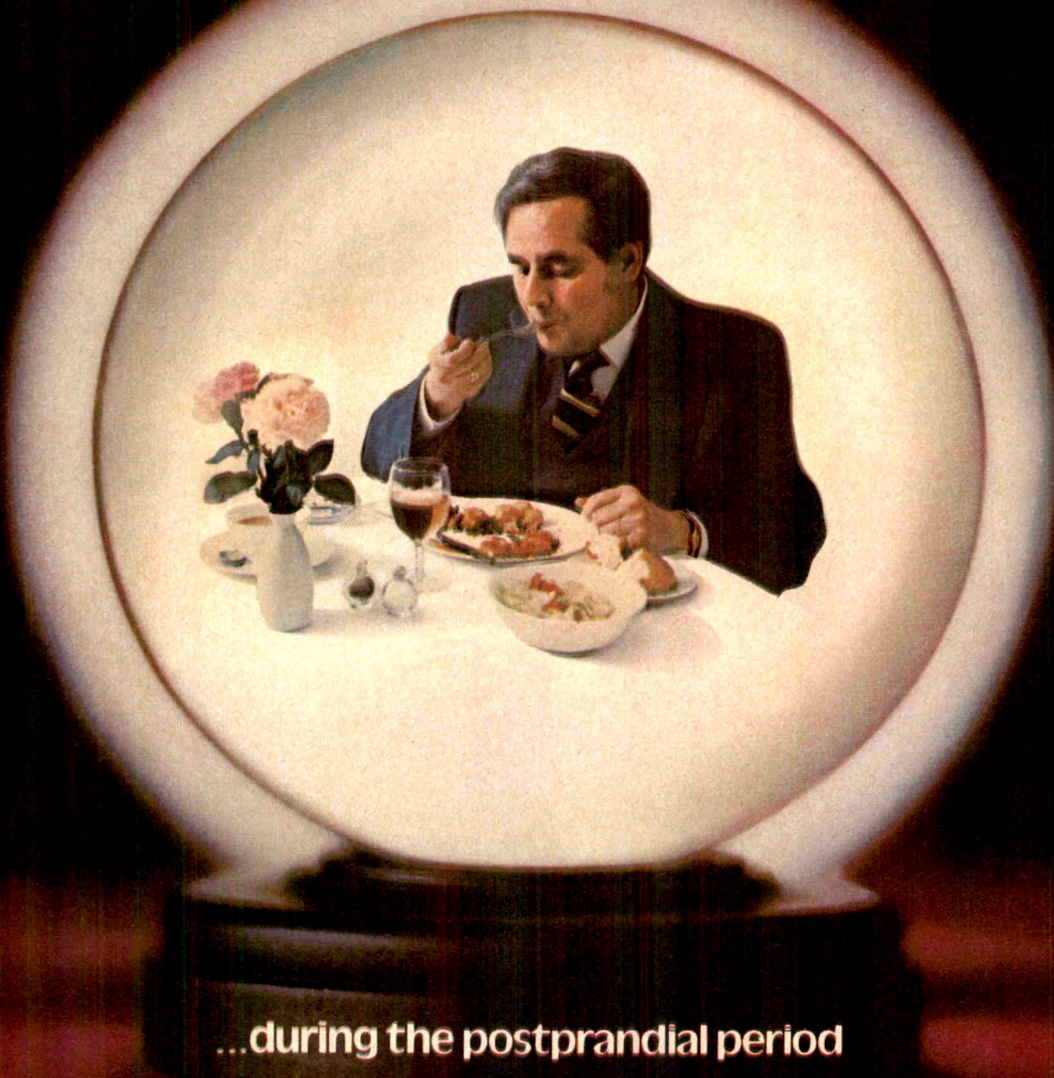
843 Favorable Effects of Oral Maintenance Digoxin Therapy on Left Ventricular Performance in Normal Subjects: Echocardiographic Study

MICHAEL H. CRAWFORD, JOEL S. KARLINER, ROBERT A. O'ROURKE *with the technical assistance of* K. WRAY AMON

Oral maintenance digoxin therapy causes a modest but highly significant improvement in left ventricular performance after acute pressure loading in normal subjects as a result of improved systolic shortening of the myocardium. During digoxin therapy mean left ventricular ejection fraction increased from 74 ± 2 to 79 ± 1 percent, left ventricular minor dimension increased from 37 ± 2 to 41 ± 1 percent and the mean rate of left ventricular dimension shortening increased from 5.66 ± 0.22 to 6.31 ± 0.23 cm/sec. These data point to a positive inotropic effect on the normal left ventricle during long-term oral digoxin therapy.

Continued on page A13

IN PREDICTABLE ANGINA*



...during the postprandial period

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.

Duration of Effect: One to two hours.

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CONTENTS

848 Electrophysiologic Effects of Atropine on Sinus Node and Atrium in Patients With Sinus Nodal Dysfunction

RAMESH C. DHINGRA, FERNANDO AMAT-Y-LEON, CHRISTOPHER WYNDHAM, PABLO DENES, DELON WU, RONALD H. MILLER and KENNETH M. ROSEN

Electrophysiologic studies performed with atrial simulation techniques before and after intravenous injection of atropine in 21 patients with sinus nodal dysfunction showed shortening of sinus cycle length and sinus recovery time after atropine as in patients without sinus nodal dysfunction; effects were only insignificant on sinoatrial conduction and atrial refractoriness. These results suggest that perinodal and atrial electrophysiologic properties may be altered in subjects with sinus node disease.

856 Vein Graft Patency and Intimal Proliferation After Aortocoronary Bypass: Early and Long-Term Angiopathologic Correlations

GERALD M. LAWRIE, J. T. LIE, GEORGE C. MORRIS, Jr. and H. LISTON BEAZLEY

As this study of 492 vein grafts from 281 patients shows, most graft occlusions after aortocoronary bypass occur early, mainly in the first 3 postoperative months, and are usually due to thrombosis. Late graft occlusion is uncommon and rarely due to intimal proliferation. The angiographic appearance of vein grafts up to 75 months postoperatively indicates that intimal proliferation is not always progressive and that moderate to severe proliferation is compatible with good graft patency.

863 Chest Pain as a Predictor of Coronary Artery Disease in Patients With Obstructive Aortic Valve Disease

PHILLIPE A. PAQUAY, GORDON ANDERSON, HELMUT DIEFENTHAL, LEONARD NORDSTROM, HAROLD G. RICHMAN and FREDARICK L. GOBEL

In this study of 76 consecutive candidates for aortic valve replacement, those without chest pain or electrocardiographic evidence of infarction were likely to be free of significant coronary artery disease. Although presence of chest pain did not predict presence of coronary artery disease, patients with more typical angina pectoris were more likely to have significant coronary artery disease. Most patients with typical angina and significant coronary artery disease had lesions in the left coronary artery.

EXPERIMENTAL STUDIES

870 Dynamic Changes in Left Ventricular Wall Thickness and Their Use in Analyzing Cardiac Function in the Conscious Dog

SHIGETAKE SASAYAMA, DEAN FRANKLIN, JOHN ROSS, Jr., WILLIAM S. KEMPER and DANIEL McKOWN

Measurements of left ventricular free wall thickness and internal chamber diameter in normal conscious dogs with use of pairs of ultrasonic crystals revealed an abrupt decrease in wall thickness with the onset of atrial contraction during the resting state, no change during isovolumic systole or with ejection, and thickening by 31.3 percent during diastole. This study also showed that a single transmural area of the left ventricular free wall can be used

Continued on page A17


In hypertensio

Hygroton® 50 mg.
(chlorthalidone)
blocks sodium retention longer

Diuretics reduce blood pressure by blocking sodium retention to lower "effective" volume. But the body's renal compensatory mechanisms are mobilized to promote a secondary sodium conservation, expand "effective" volume and perhaps reelevate blood pressure. Sustained control of "effective" volume is therefore essential to treatment. No other diuretic blocks sodium retention longer than Hygroton.

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a "24-hour sentry" effect

Enhances patient compliance

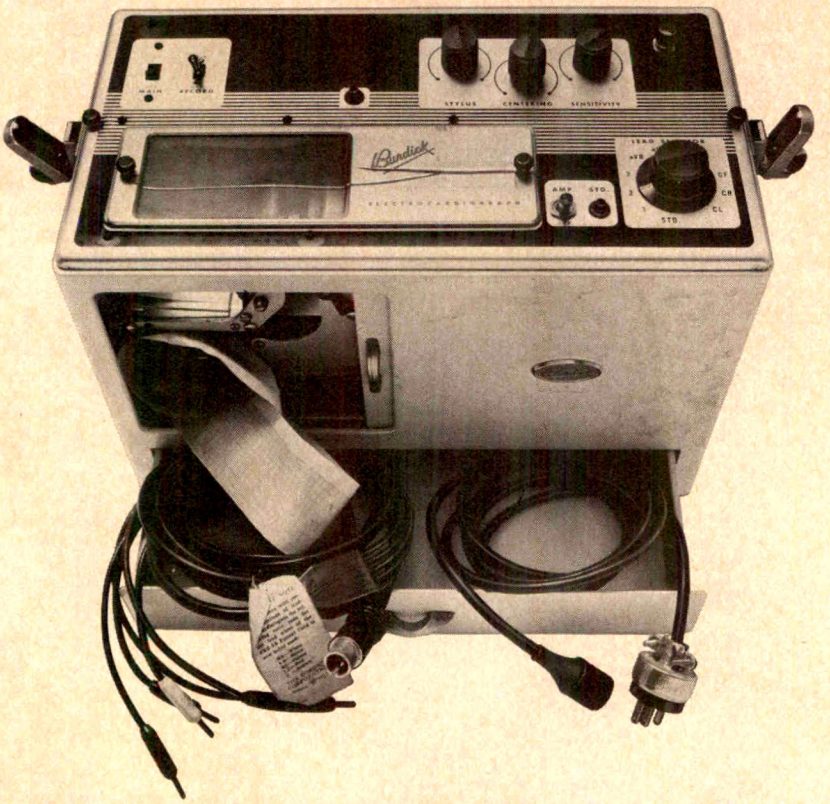
The "24-hour sentry" effect of Hygroton allows once-a-day administration. This uncomplicated regimen encourages patient compliance through simplicity and economy. Proven efficacy and compliance have made Hygroton one of the most widely prescribed diuretic/antihypertensives for mild to moderate hypertension today.

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BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone; routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May be additive or potentiative of the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Usage in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in cord blood and breast milk. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

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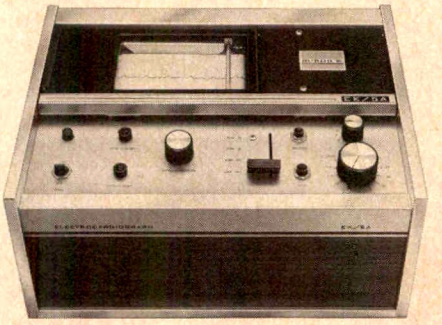
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to reflect myocardial function and overall left ventricular dynamics in the absence of regional dysfunction. Such studies carried out during atrial pacing, after administration of drugs, during acute coronary occlusion and during chronic pressure overloading constitute a new approach to the assessment of cardiac function that has potential echocardiographic applications.

880 **Coronary Steal: Its Role in Detrimental Effect of Isoproterenol After Acute Coronary Occlusion in Dogs**

MICHAEL V. COHEN, EDMUND H. SONNENBLICK and EDWARD S. KIRK

This study in 10 dogs demonstrates that isoproterenol, in addition to its inotropic effect, aggravates ischemia distal to a coronary occlusion by decreasing collateral blood flow. This decrease is produced by a coronary steal and by a reduction in coronary perfusion pressure. Any agent causing primary or secondary coronary vasodilatation may cause a coronary steal and enhance myocardial injury.

889 **Preceding His-Atrial Interval as a Determinant of Atrioventricular Nodal Conduction Time in the Human and Rabbit Heart**

JACQUES BILLETTE

Conduction time through the atrioventricular (A-V) node in the human and the isolated rabbit heart depends mainly upon the length of the preceding His-atrial (H-A) interval. When the H-A interval is taken as an indicator of the resting period of the A-V node, A-V conduction is only slightly influenced and mainly facilitated by the cumulative effects of frequency at faster basic rates. This facilitation is compatible with similar frequency-dependent shortening of the functional refractory period of the A-V node.

PEDIATRIC CARDIOLOGY

897 **Double Outlet Left Ventricle. Morphology, Cineangiocardiographic Diagnosis and Surgical Treatment**

PETER W. T. BRANDT, A. LOUISE CALDER, BRIAN G. BARRATT-BOYES and JOHN M. NEUTZE

This report discusses the anatomic and cineangiocardiographic features of five patients with double outlet left ventricle, the classification and diagnosis of connection disorders, and the diagnostic radiologic criteria. The radiographic diagnosis can be established only by delineating the relations of the origin of the great artery to the ventricular septum using the radiologic projection (usually left anterior oblique) that profiles the ventricular septum. The surgical significance of these anatomic features is discussed.

910 **Congenitally Corrected Transposition of the Great Arteries: Morphologic Study of 32 Cases**

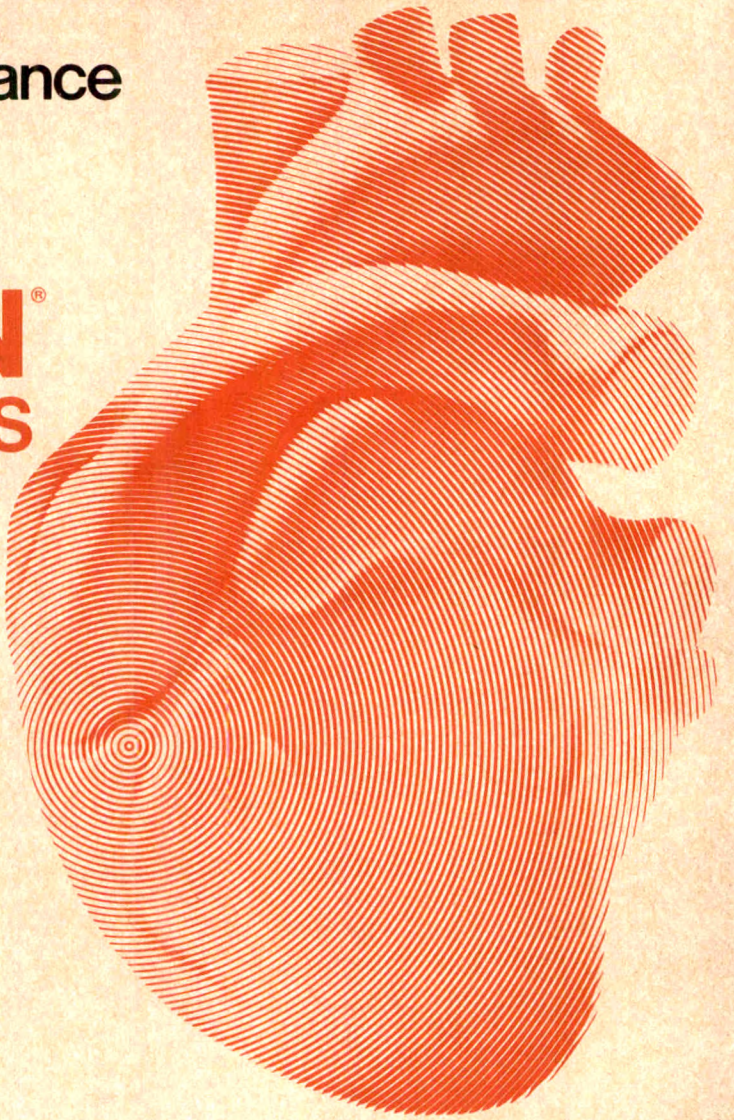
SALLY P. ALLWORK, HUGH H. BENTALL, ANTON E. BECKER, HUGH CAMERON, LEON M. GERLIS, JAMES L. WILKINSON and ROBERT H. ANDERSON

Thirty-two autopsy cases of congenitally corrected transposition of the great arteries (combination of atrioventricular [A-V] discordance and transposition of the great arteries) are comprehensively described; special attention is paid to possible surgical approaches for repair of the anomalies. Particular attention must be given to the precise anatomy and disposition of the mitral valve apparatus, the coronary arteries and the conducting tissues, as well as to anomalies of the tricuspid valve, ventricular septal defect and pulmonary outflow tract obstruction.

Continued on page A19

The Pacekeeper™

For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance



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BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

CONTENTS

SPECIAL STUDY

924 **Candida Myocarditis Without Valvulitis**

WILLIAM G. FRANKLIN, ARTHUR B. SIMON and THOMAS M. SODEMAN

The frequency of Candida infections is increasing, particularly in patients with blood dyscrasias. In this series 31 of 50 patients (62 percent) with systemic candidiasis had myocardial involvement at postmortem examination. Candida invasion of the heart should be suspected when a young person without preexistent heart disease has positive cultures for a Candida organism and a significant cardiac arrhythmia, conduction disturbance or other sudden QRS changes in the electrocardiogram. The effect of therapy is unknown.

REPORTS ON THERAPY

929 **Intramuscular Clindamycin for Therapy of Infective Endocarditis. Report of 23 Cases and Review of the Literature**

KEITH H. BURCH, EDWARD L. QUINN, FRANK COX, TOM MADHAVAN, EVELYN FISHER and DONALD ROMIG

Successful treatment of 21 of 23 patients with infective endocarditis demonstrates that intramuscular clindamycin has a limited but valuable use as an alternate agent in such patients allergic to penicillin. Thirteen patients had Staphylococcus aureus endocarditis and 11 of the infections were heroin-related and involved the tricuspid valve. Although clindamycin can be useful in streptococcal endocarditis, it should be used with caution since it is less bactericidal than the penicillins or cephalosporins and organisms have become resistant during treatment with it.

934 **Clinical Efficacy of Amiodarone as an Antiarrhythmic Agent**

MAURICIO B. ROSENBAUM, PABLO A. CHIALE, M. SUSANA HALPERN, GERARDO J. NAU, JULIO PRZYBYLSKI, RAÚL J. LEVI, JULIO O. LÁZZARI and MARCELO V. ELIZARI

Amiodarone given orally in doses of 200 to 600 mg/day proved very effective in the treatment and prevention of arrhythmias, totally suppressing and controlling supraventricular arrhythmias in 98 (92.4 percent) of 106 patients and ventricular arrhythmias in 119 (82 percent) of 145 patients. It proved safe in patients with severe congestive heart failure and myocardial damage, and had a wide safety margin and cumulative effect. Its most important undesirable side effect is reversible corneal microdeposits and its most important contraindication is intraventricular or atrioventricular block.

REVIEWS

945 **Spectrum of Coronary Arterial Spasm. Clinical, Angiographic and Myocardial Metabolic Experience in 29 Cases**

LESLIE WIENER, HRATCH KASPARIAN, PETER R. DUCA, PAUL WALINSKY, RONALD S. GOTTLIEB, FRANCES HANCKEL and ALBERT N. BREST

Coronary arterial spasm was observed angiographically in 29 patients, including 7 patients with normal-appearing coronary arteries and 22 with various degrees of stenosis. During spasm the hemodynamic findings were those of a hypodynamic state, in contrast to findings in patients with typical exertional angina. These 29 cases, detected over a 2 year peri-

od in 3,000 consecutive coronary angiographic studies, reflect a 1 percent incidence rate of coronary spasm. Patients with spasm manifest an atypical anginal syndrome complicated by cardiac arrhythmias (including atrioventricular block and ventricular fibrillation), myocardial infarction and death. They respond less favorably to coronary bypass surgery than those with definite coronary arteriosclerosis.

CASE REPORTS

956 **Afterload Reduction in the Management of Postinfarction Ventricular Septal Defect**

PAUL L. TECKLENBERG, JOHN FITZGERALD, BASIL I. ALLAIRE, EDWIN L. ALDERMAN and DONALD C. HARRISON

In two patients afterload reduction with intravenously administered nitroprusside or sublingually administered isosorbide dinitrate with careful hemodynamic monitoring demonstrated that such therapy is a potentially useful adjunct in the medical management of ventricular septal defect complicating acute myocardial infarction. Improving cardiac function in this way for 4 to 8 weeks makes surgical repair easier and safer. The principal benefit of these agents is improved systemic blood flow without significant change in blood pressure.

959 **Pulmonary Arterial Compression Syndrome Caused by False Aneurysm of Left Ventricular Outflow Tract**

MICHAEL J. COWLEY, JAMES L. WELLS, Jr., WILLIAM P. HOOD, Jr. and JOHN W. KIRKLIN

An unusual false aneurysm of the left ventricular outflow tract just under the aortic ring, arising from an anular excavation related to previous endocarditis with abscess formation, caused extrinsic compression of the right pulmonary artery and pulmonary hypertension. The ostium of the aneurysm was successfully closed by oversewing during insertion of a Bjork-Shiley aortic valve prosthesis.

SPECIAL DEPARTMENTS

964 **Letters to the Editor**

Lymphatics and Myocardial Infarction—A. J. Miller and A. J. Libanoff

Prinzmetal's Variant Angina—R. MacAlpin and C. B. Higgins

966 **American College of Cardiology News**

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970 **Subject Index**



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Other Features

Electrical interference protection is provided by highly selective input filters in the pacemaker and complete titanium encapsulation. As an additional safety measure, the pacemaker automatically switches from the QRS-inhibited mode to the basic rate mode in the event of unusually strong fields of interference.

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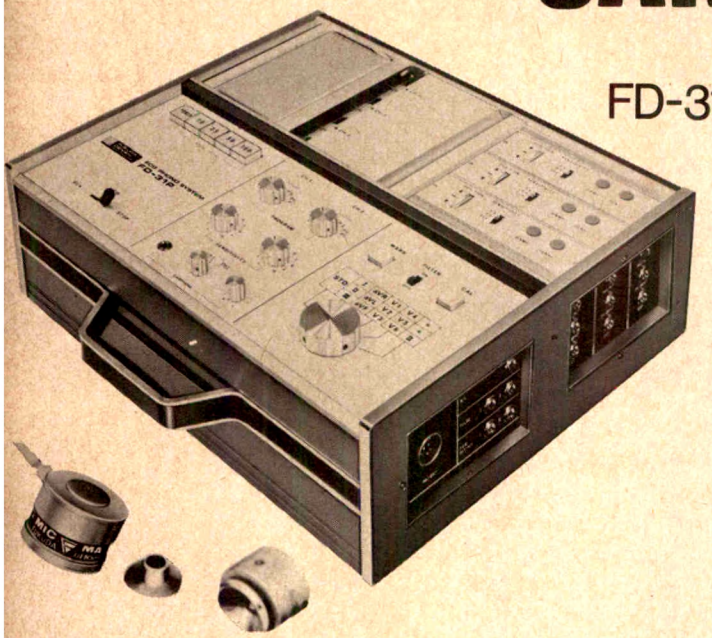
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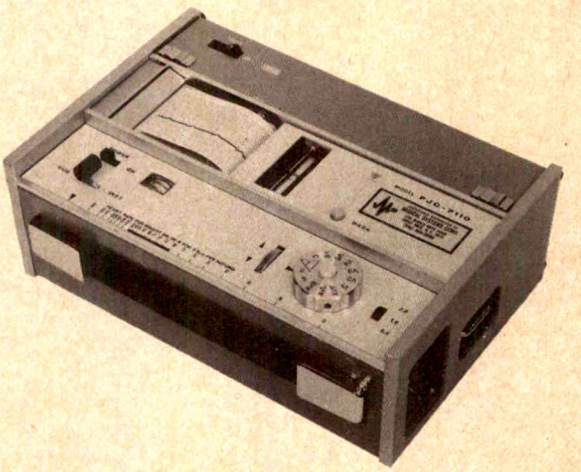
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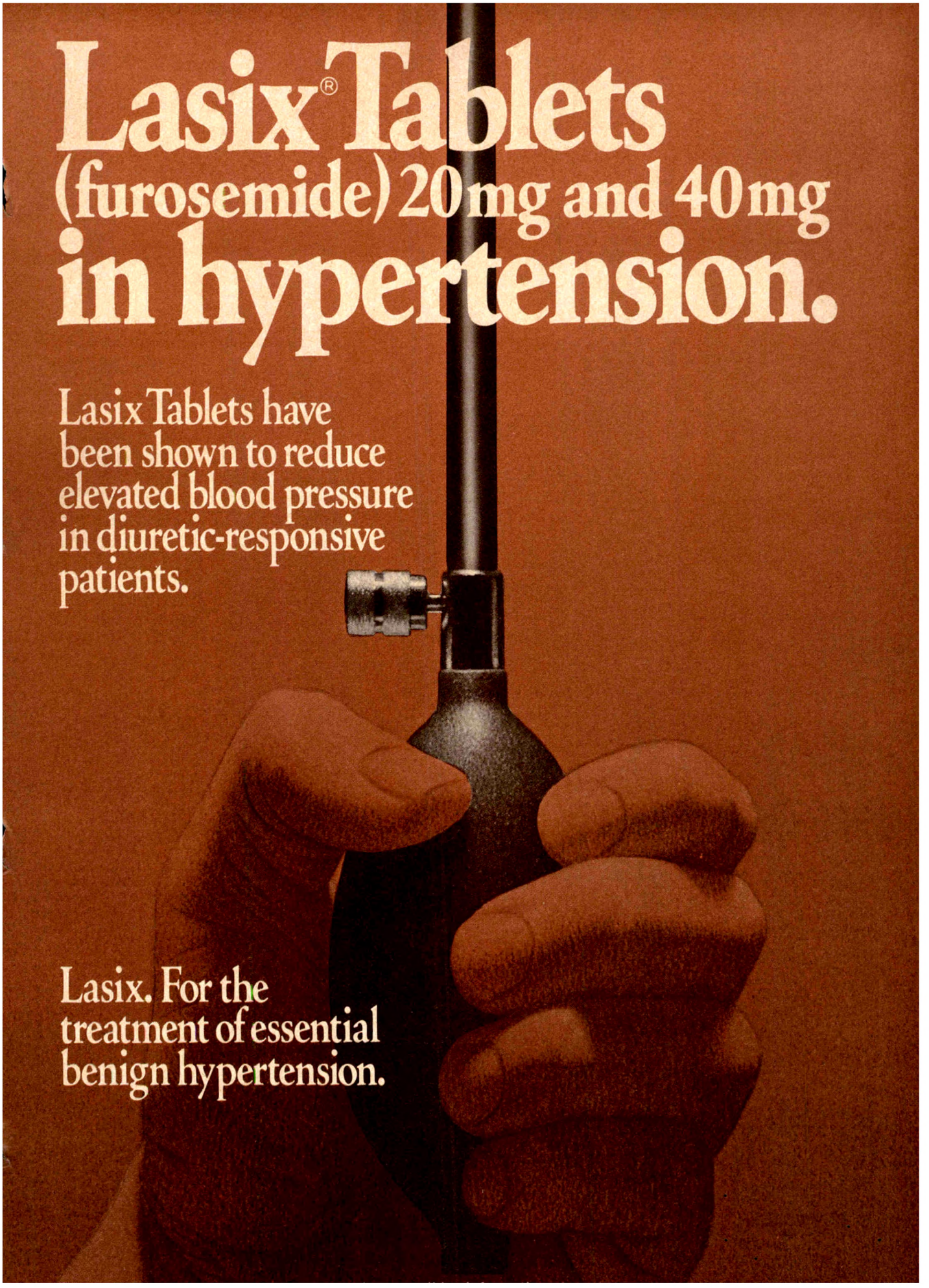
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Lasix® Tablets (furosemide) 20 mg and 40 mg in hypertension.

A brief summary of the Prescribing Information for

Lasix® (furosemide) Tablets 20 mg and 40 mg

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

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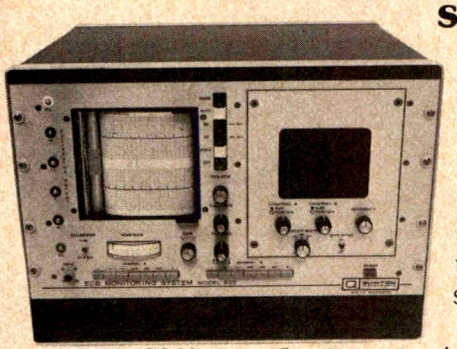
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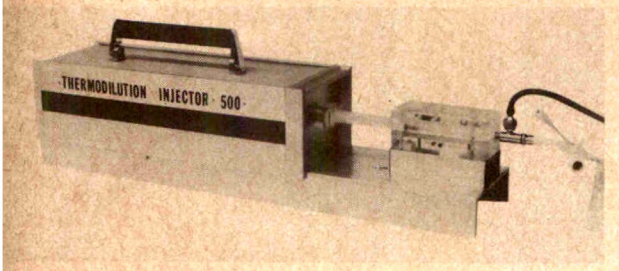

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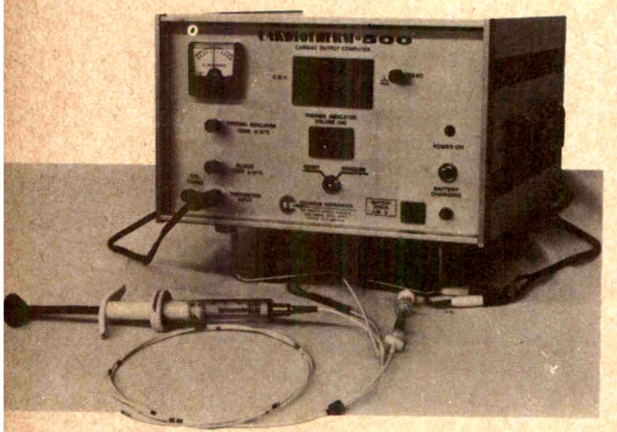


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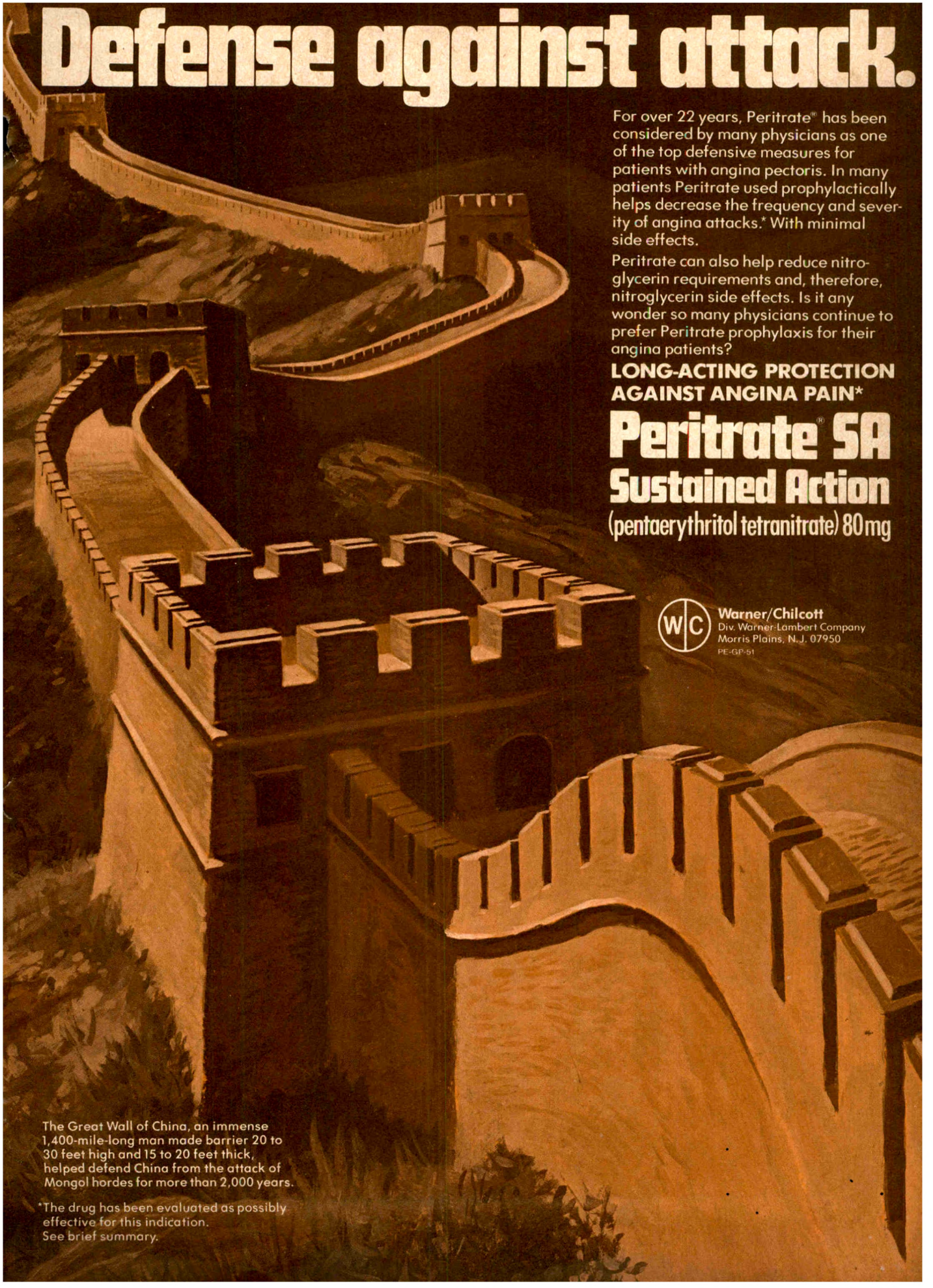


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See brief summary.

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HYPERSTAT® I.V. (brand of diazoxide, USP) Injection

FOR INTRAVENOUS USE IN HOSPITALIZED PATIENTS ONLY

INDICATIONS For the emergency reduction of blood pressure in malignant hypertension in hospitalized patients, when prompt and urgent decrease of diastolic pressure is required. Treatment with orally effective antihypertensive agents should be instituted as soon as the hypertensive emergency is controlled. HYPERSTAT I.V. Injection is ineffective against hypertension due to pheochromocytoma.

CONTRAINDICATIONS It should not be used in the treatment of compensatory hypertension, such as that associated with aortic coarctation or arteriovenous shunt, nor in patients hypersensitive to diazoxide or other thiazides, unless the potential benefits outweigh the possible risks.

WARNINGS Safety in pregnancy and in children has not yet been established. Information is not available concerning the passage of HYPERSTAT in breast milk. However, it is known that diazoxide crosses the placental barrier and appears in cord blood. Like other thiazides, the drug may produce fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism, and possibly other adverse reactions that have occurred in adults. Hypotension may occasionally result. If severe enough to require therapy, it will usually respond to the administration of sympathomimetic agents, such as norepinephrine. Hyperglycemia occurs in the majority of patients, but usually requires treatment only in patients with diabetes mellitus; it will respond to the usual management, including insulin. Therefore, blood glucose levels should be monitored, especially in patients with diabetes or in those requiring multiple injections of diazoxide. Hyperglycemia and hyperosmolar coma associated with transient cataracts developed in one infant receiving repeated daily doses of oral diazoxide. The disturbed carbohydrate metabolism was successfully treated with insulin. Cataracts have been observed in a few animals receiving repeated daily doses of intravenous or oral diazoxide. Since diazoxide causes sodium retention, repeated injections may precipitate edema and congestive heart failure. This retention responds characteristically to diuretic agents if adequate renal function exists. Concurrently administered thiazides may potentiate the antihypertensive, hyperglycemic, and hyperuricemic actions of diazoxide (See Drug Interactions). Since increased volume of extracellular fluid may be a cause of treatment failure in nonresponsive patients, it may be advisable to reduce this increased volume by means of a diuretic agent. Although no evidence of excessive anticoagulant effects has been reported, patients, especially those who are hypoalbuminemic and receive HYPERSTAT I.V. Injection and coumarin or its derivatives, may require reduction in dosage of the anticoagulant (See Drug Interactions).

PRECAUTIONS HYPERSTAT (diazoxide) I.V. Injection is a potent antihypertensive agent requiring close monitoring of the patient's blood pressure at frequent intervals. Its administration may occasionally cause hypotension requiring treatment with sympathomimetic drugs. Therefore, adequate facilities to treat such untoward reactions should be available. It should be administered only into a peripheral vein. Because the alkalinity of the solution is irritating to tissue, extravascular injection or leakage should be avoided; subcutaneous administration has produced inflammation and pain without subsequent necrosis. If leakage into subcutaneous tissue occurs, the area should be treated conservatively. Maximal antihypertensive effects occur after rapid administration (within 30 seconds) into the vein; a slower injection may fail to reduce blood pressure or produce a very brief response. As with any potent antihypertensive agent, HYPERSTAT I.V. Injection should be used with care in patients who have impaired cerebral or cardiac circulation, that is, patients in whom abrupt and brief reductions in blood pressure might be detrimental. Special attention is required for patients with diabetes mellitus and those in whom retention of salt and water may present serious problems (See Warnings). Nondiabetic patients may have a transient, reversible, and clinically insignificant increase in blood glucose following HYPERSTAT I.V. Injection. Since peritoneal dialysis or hemodialysis can reduce levels of diazoxide in the blood, patients undergoing dialysis may require more than one injection.

ADVERSE REACTIONS

Frequent and serious adverse reactions: Sodium and water retention after repeated injections, especially important in patients with impaired cardiac reserve; hyperglycemia frequently requiring treatment in diabetic patients, especially after repeated injections.

Infrequent but serious adverse reactions: Hypotension to shock levels; myocardial ischemia, usually transient but possibly leading to thrombosis and manifested by angina, atrial and ventricular arrhythmias, and marked electrocardiographic changes; cerebral ischemia, usually transient but possibly leading to thrombosis and manifested by unconsciousness, convulsions, paralysis, confusion or focal neurological deficit, such as numbness of the hands; persistent retention of nitrogenous wastes after repeated injections; sensitivity reactions, such as rash, leukopenia, and fever. Rarely, acute pancreatitis has been reported. Papilledema, induced by plasma volume expansion secondary to the administration of diazoxide, was reported in one patient who had received eleven injections over a twenty-two day period.

Other adverse reactions: Vasodilative phenomena, such as orthostatic hypotension, sweating, flushing, and generalized or localized sensations of warmth; supraventricular tachycardia and palpitation; bradycardia; various transient neurological findings secondary to alterations in regional blood flow to the brain, such as headache (sometimes throbbing), dizziness, lightheadedness, sleepiness (also reported as lethargy, somnolence or drowsiness), euphoria or "funny feeling", ringing in the ears and momentary hearing loss, and weakness of short duration; chest discomfort or nonanginal "tightness in the chest"; transient hyperglycemia in nondiabetic patients; transient retention of nitrogenous wastes; and various respiratory and gastrointestinal findings, secondary to the relaxation of smooth muscle, such as dyspnea, cough and choking sensation; nausea and vomiting and/or abdominal discomfort, anorexia, alteration in taste, parotid swelling, salivation, dry mouth, lacrimation, ileus, constipation and diarrhea. Also, warmth or pain along the injected vein; cellulitus without sloughing and/or phlebitis at the site of extravasation; back pain; and increased nocturia. Apprehension or anxiety, malaise and blurred vision occurred on single occasions.

DRUG INTERACTIONS Since diazoxide is highly bound to serum protein, it may displace other substances or drugs which are also bound to protein, such as bilirubin or coumarin and its derivatives. These potential interactions must be considered when administering HYPERSTAT I.V. Injection. The concomitant administration of diazoxide with thiazides or other commonly used potent diuretics may potentiate the hyperglycemic, hyperuricemic, and antihypertensive effects of diazoxide.

OVERDOSAGE Overdosage may cause an undesirable hypotension. Usually, this can be controlled with sympathomimetic agents, such as norepinephrine; failure of the blood pressure to rise in response to such an agent suggests that the hypotension may have been caused by something other than diazoxide. Excessive hyperglycemia resulting from overdosage will respond to conventional therapy of hyperglycemia. Diazoxide may be removed from the blood by peritoneal dialysis or hemodialysis.

SWW-4940R1

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"The injection of the [diazoxide] bolus in 10 to 15 seconds results in a prompt blood pressure fall in a high percentage of cases. A maximal blood pressure response usually occurs within 5 to 10 minutes."*

☐ Rapid reduction to normotensive levels

Induces rapid reduction of blood pressure generally within 5 minutes...often in 1 or 2 minutes to the lowest level achieved. Blood pressure response facilitated by appropriate diuretic therapy.

☐ Prolonged activity

A single injection of HYPERSTAT I.V. generally maintains blood pressure below pretreatment levels for periods up to 12 hours.

☐ Protective action—helps avert target organ damage

Cardiac output increases as diastolic pressure is reduced. Coronary and cerebral blood flow maintained. Increased renal blood flow after transient decrease.

☐ Uncomplicated procedure

Simple I.V. "push" in a peripheral vein in 30 seconds or less. Close monitoring at frequent intervals is necessary until blood pressure is stabilized (generally 15-30 minutes). Thereafter, hourly measurement should be taken during the balance of effect.

☐ Convenient...no preparation

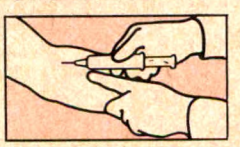
HYPERSTAT I.V. supplied as a 20 ml ampule containing 300 mg diazoxide in ready to use solution.

*Marvin Moser, M.D., Assistant Professor of Clinical Medicine, Albert Einstein College of Medicine, and Chief of Cardiology, White Plains Hospital, White Plains, N.Y., in Diazoxide—an effective vasodilator in accelerated hypertension. *Am Heart J 87*(6): 791-795, June 1974.

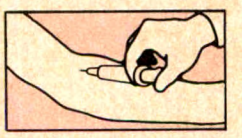
Administration guidelines



1. Fill dry syringe with appropriate dose of HYPERSTAT I.V. Injection (20 ml ampule contains 300 mg diazoxide).



2. Hospitalized patient should be recumbent. Insert needle only into a peripheral vein.



3. Inject entire dose I.V. in 30 seconds or less. Remove needle carefully—avoid extravasation.

4. Keep patient recumbent for at least half an hour after injection; monitor BP closely until stabilized—usually 15-30 minutes.

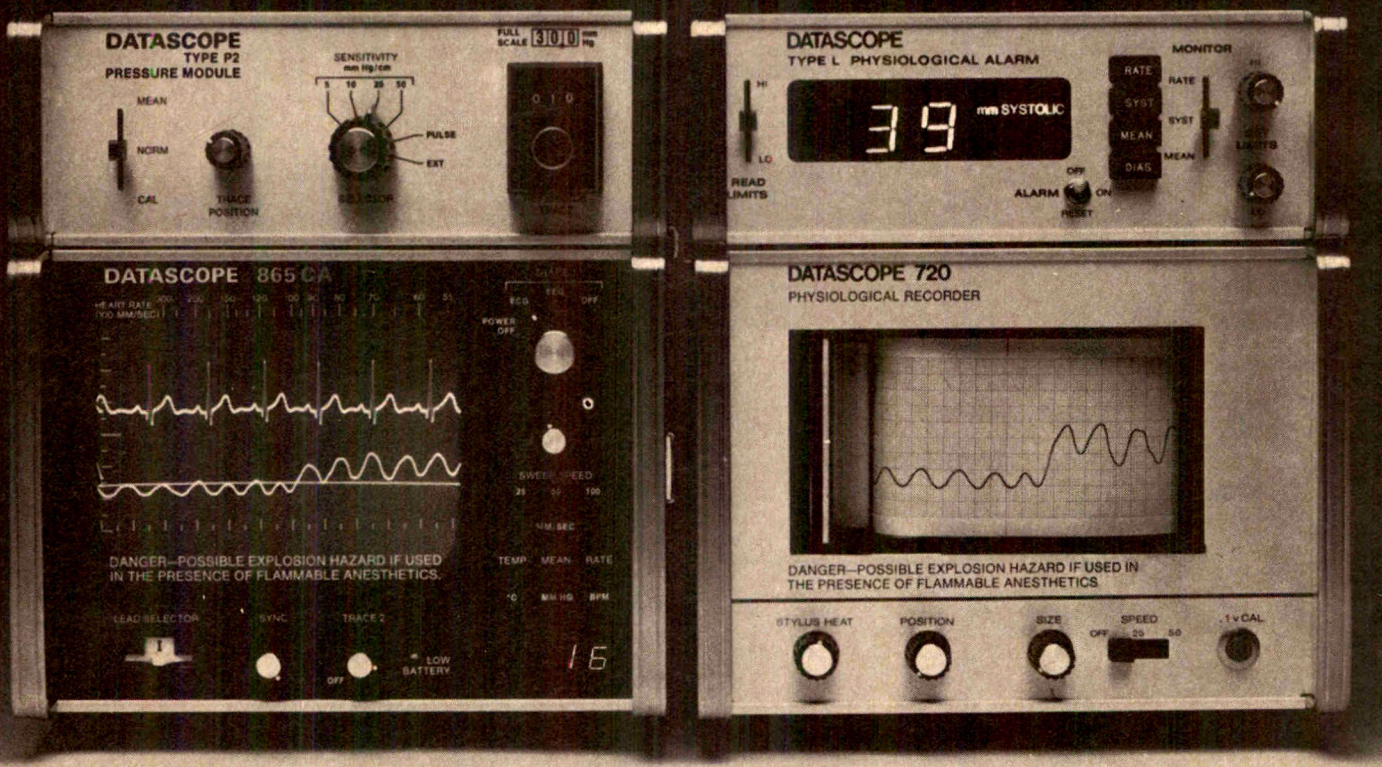
5. If patient is to be ambulatory, measure BP in standing position before ending surveillance.

6. HYPERSTAT I.V. Injection should be continued until a regimen of oral antihypertensive medication becomes effective (generally within a few days).

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Before prescribing HYPERSTAT I.V. Injection, please consult complete product information a summary of which appears on the facing page.

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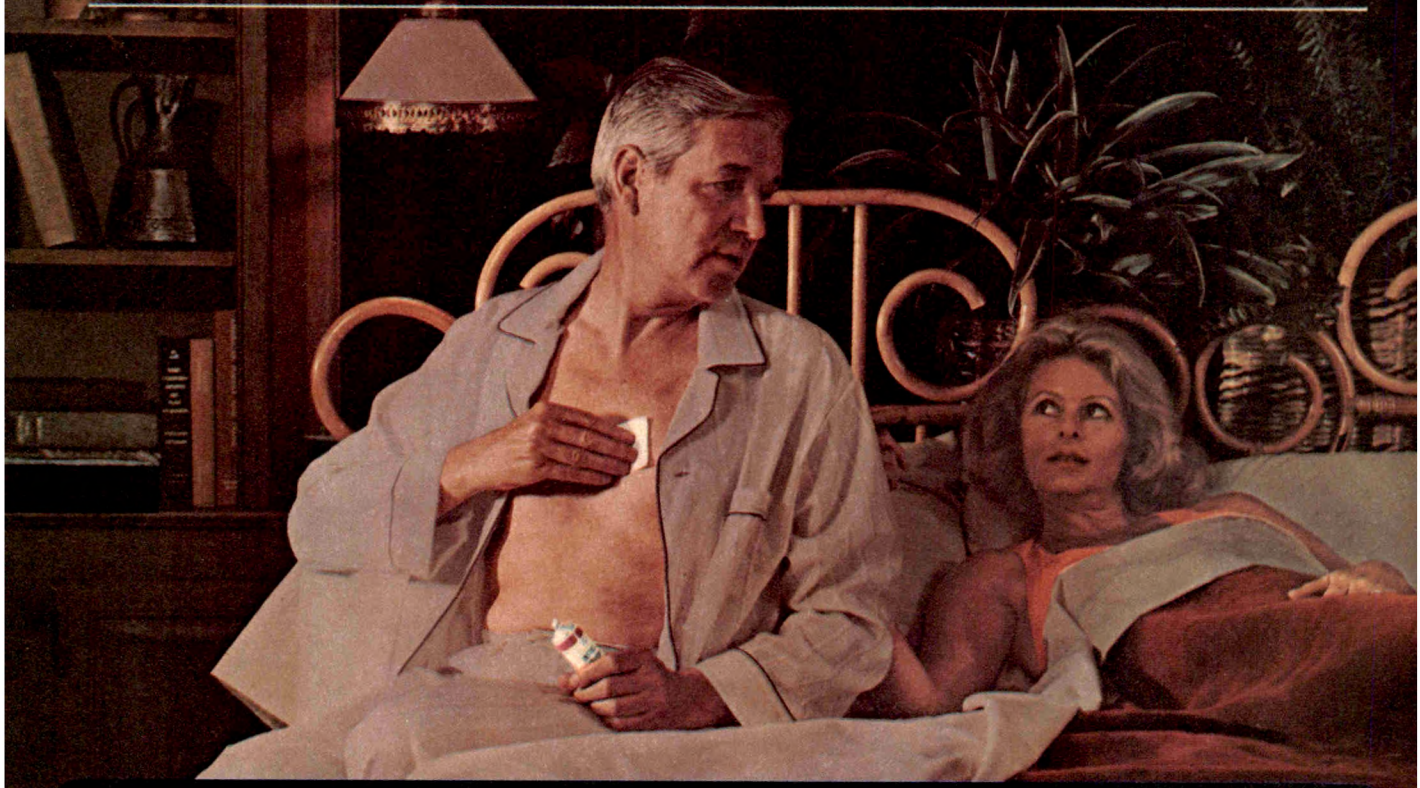
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DOSAGE AND ADMINISTRATION: Usual dose is 1-2 inches, as squeezed from tube. Some patients require 4-5 inches. To determine optimal dosage, start with 1 inch, increase dose 1/2 inch at a time until headache occurs, then drop back to largest dose which doesn't cause headache. Apply to desired skin area with Dose Measuring Applicator. DO NOT USE FINGERS. Spread in thin, uniform layer. May be applied every 3-4 hours if necessary. Effective in control of angina pectoris, regardless of skin site of application, although patients may prefer chest site because anginal pain originates in this area. To stop treatment of anginal patients, gradually reduce dosage and frequency of application over period of 4-6 weeks to prevent characteristic nitroglycerin withdrawal reactions.
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REFERENCES: 1. Davidov ME, Mroczek WJ: The effect of nitroglycerin ointment on the exercise capacity in patients with angina pectoris. *Angiology* 27:205-211 (April) 1976. 2. Data on file, Department of Medicine, Marion Laboratories, Inc., Kansas City, Missouri.


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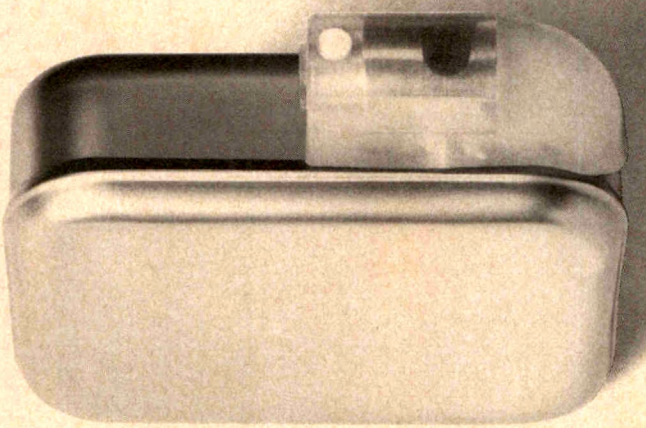
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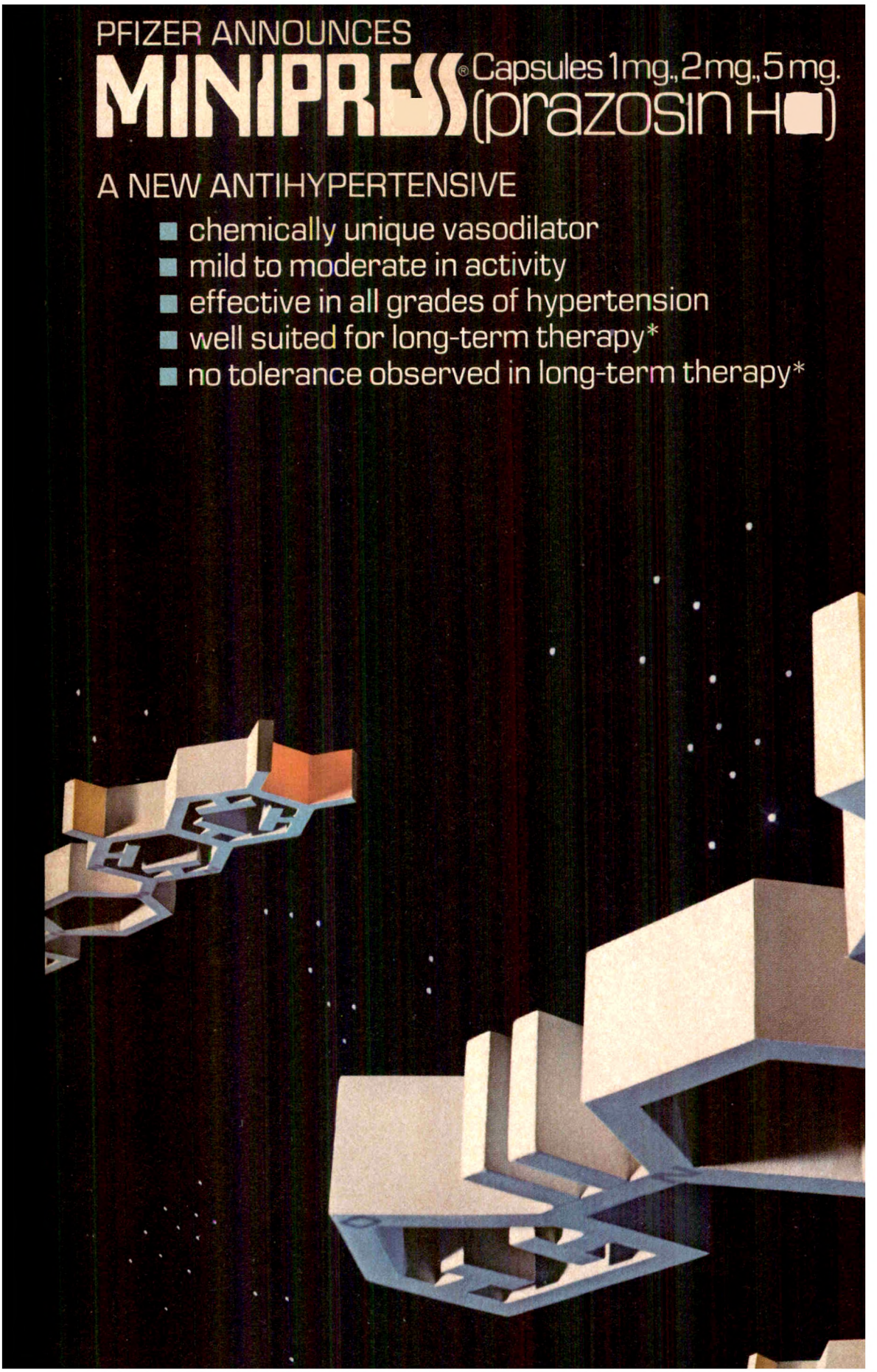
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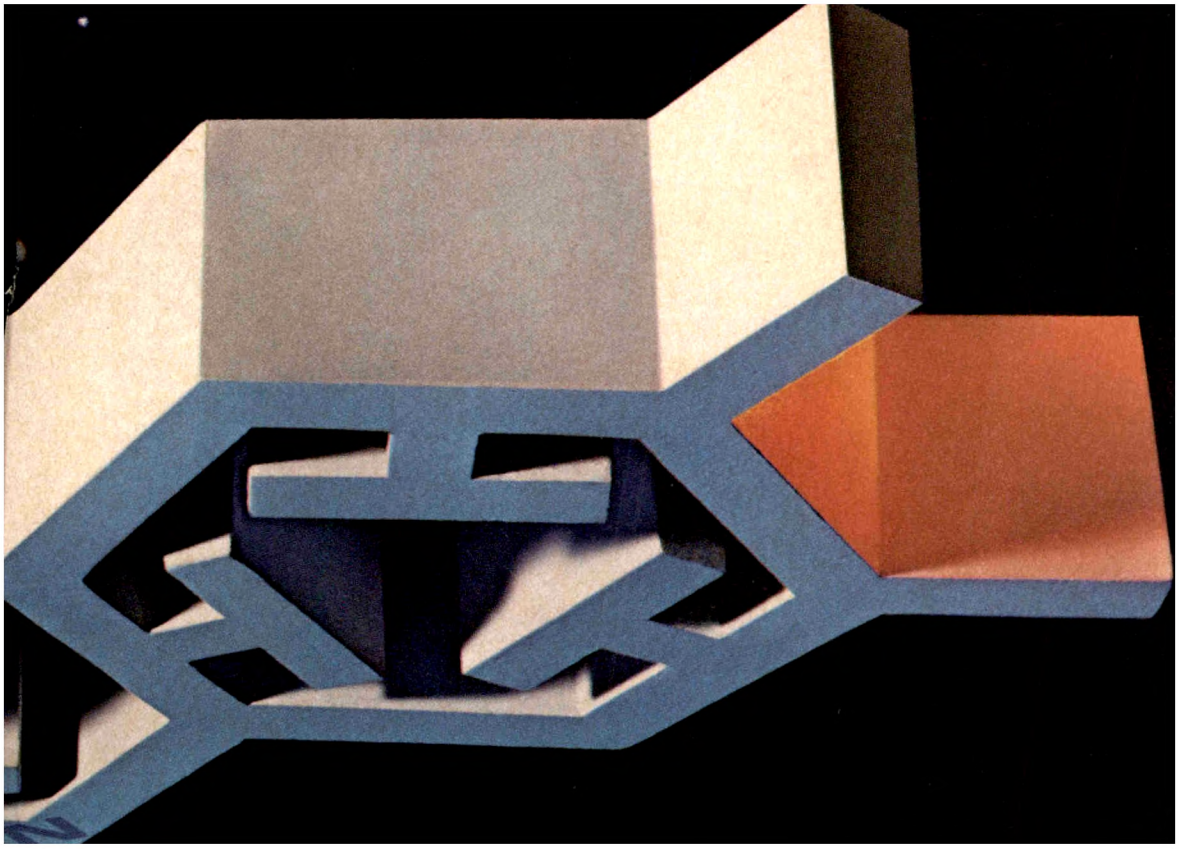
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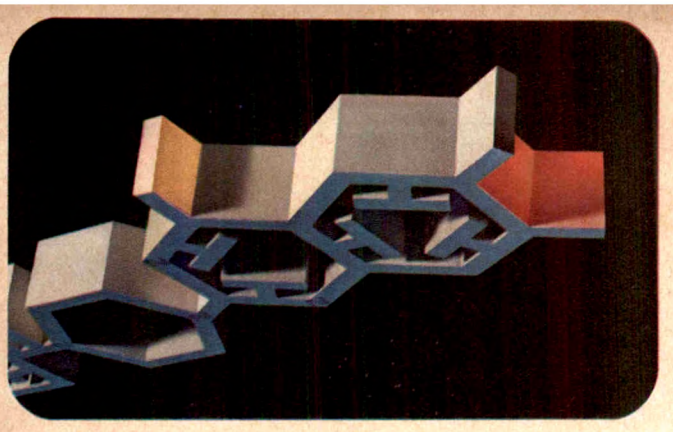
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A NEW ANTIHYPERTENSIVE
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mild to moderate in activity
effective in all grades of hypertension
well suited for long-term therapy*
no tolerance observed in long-term therapy*





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- No tolerance observed in long-term therapy in patients on continuous therapy for periods of up to 5 years.
- Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.
- Side effects most frequently experienced with Minipress in a series of 934 patients were: dizziness (10.3%), headache (7.8%), drowsiness (7.6%), lack of energy (6.9%), weakness (6.5%), palpitations (5.3%), and nausea (4.9%). A small percentage of patients have experienced orthostatic hypotension (3.4%) and syncope (1.3%). (For a more detailed description of orthostatic hypotension and syncope, see Warnings in Brief Summary before initiating therapy with Minipress.)
- Starting dosage: 1 mg. t.i.d.
- Usual maximum recommended dosage: 20 mg. daily, given in divided doses.
- Available in 1-mg., 2-mg., and 5-mg. capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

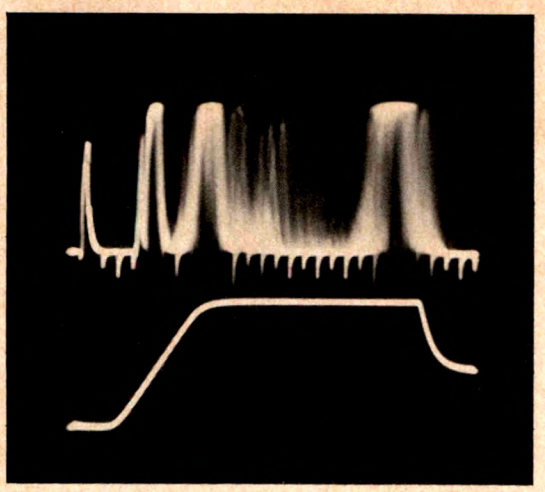
HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250.

More detailed information available on request.

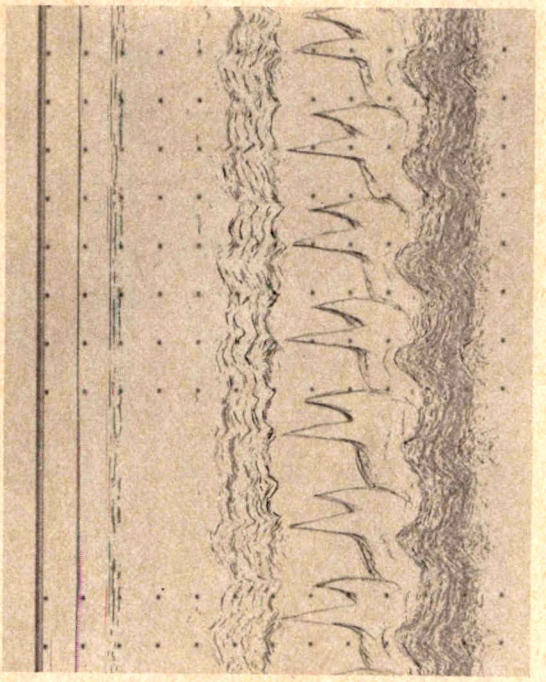
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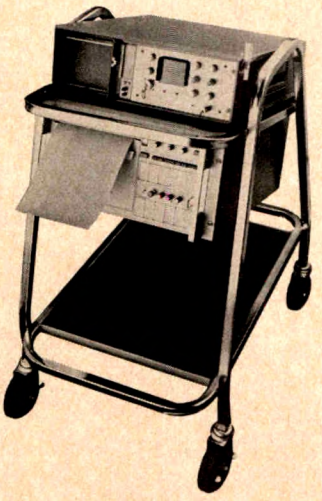


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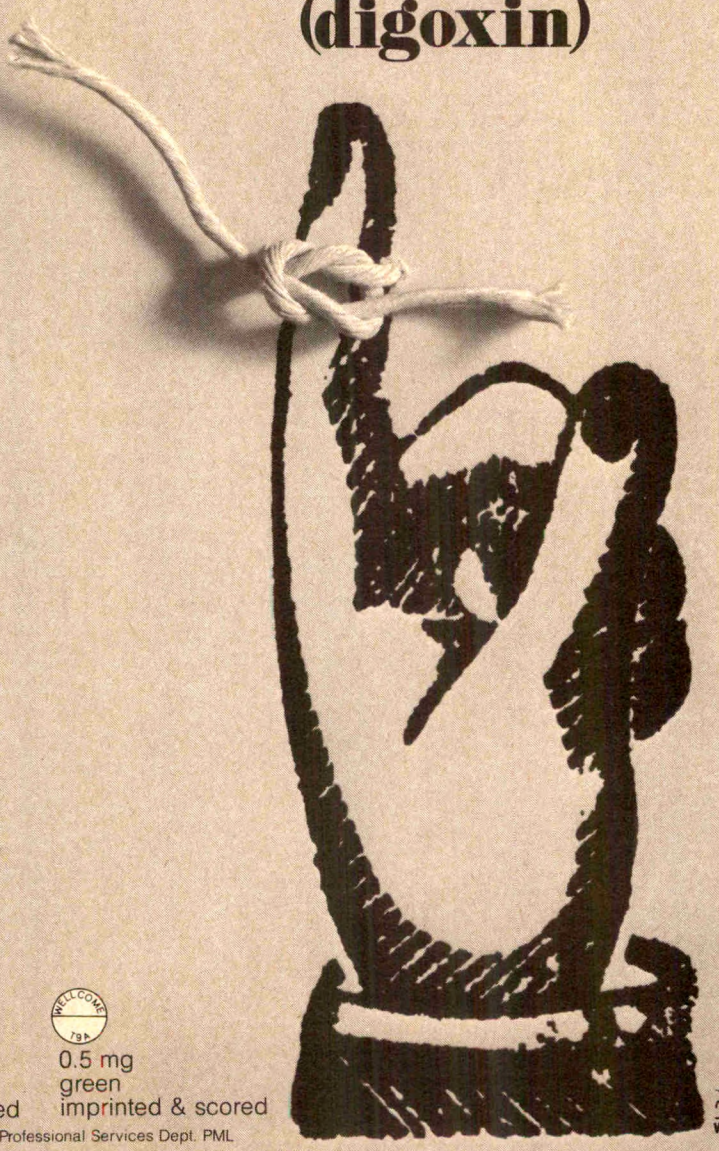
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The American Journal of CARDIOLOGY®

VOLUME 38

NUMBER 7

CLINICAL STUDIES

Left Ventricular Performance in Mitral Regurgitation Assessed With Systolic Time Intervals and Echocardiography

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ARNOLD M. WEISSLER, MD, FACC

Detroit, Michigan

Among 22 patients with isolated mitral regurgitation of various origins, systolic time intervals (preejection period [PEP] index, left ventricular ejection time [LVET] index and PEP/LVET) and echocardiographic measures of left ventricular performance (end-diastolic diameter [Dd], end-systolic diameter [Ds], and the percent change in minor axis diameter [%ΔD]) were calculated. The patients were classified into two groups, those with a normal or supernormal %ΔD (group I, 15 patients) and those with a decreased %ΔD (group II, 7 patients).

On group analysis, prolongation of the preejection period, shortening of the left ventricular ejection time and an increase in PEP/LVET was generally characteristic of patients with mitral regurgitation. These changes were accentuated when mitral regurgitation was complicated by echocardiographic evidence of diminished left ventricular contractile performance (%ΔD less than 30 percent). An increase in PEP/LVET to greater than 0.50 was consistently associated with abnormal left ventricular performance, whereas a normal PEP/LVET ratio reflected normal or supernormal left ventricular performance.

An inverse linear relation was found between PEP/LVET and %ΔD. When compared with previous data on the relation of these variables among patients without valve insufficiency, PEP/LVET proved to be increased for any level of %ΔD in mitral regurgitation. The state of digitalization did not appear to influence the relation between PEP/LVET and %ΔD. The use of echocardiographic measurements augments the determination of systolic time intervals in the analysis of left ventricular performance in patients with mitral regurgitation.

From the Department of Medicine, Wayne State University and Harper Hospital, Detroit, Mich. Manuscript received April 7, 1976; revised manuscript received June 25, 1976, accepted June 30, 1976.

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Noninvasive methods for assessing left ventricular performance are well established in conditions involving the myocardium, such as coronary artery, hypertensive and primary myocardial disease. In particular, systolic time interval determinations have been found an effective means of quantitating left ventricular performance in these conditions.[1–3] In cardiac valve disease, however, the reliability of these measurements is less clear since both the valve defect and altered left ventricular function

an alter the systolic time intervals. In mitral regurgitation the interplay of these factors is difficult to delineate. Recent studies have documented the accuracy of echocardiographic methods in assessing left ventricular chamber performance in both valve and nonvalve disease.[4–8] In view of this newer application of the echocardiographic approach, this investigation on the combined use of systolic time intervals and echocardiographic measures in evaluating left ventricular performance in mitral regurgitation was initiated.

Methods

Twenty-two patients with mitral regurgitation without other hemodynamically significant valve disease were studied (Table I). Fourteen were male and eight female; their ages ranged from 16 to 69 years. The condition was of rheumatic origin in five patients (including three with ruptured chordae tendineae found at open heart surgery). It was caused by papillary muscle dysfunction due to coronary artery disease in three, healed infective endocarditis in three and prolapse of one or more mitral valve leaflets in nine. In two patients the cause could not be established. Among the nine patients with mitral valve prolapse, the condition was confirmed with echocardiography and contrast ventriculography in seven patients and with echocardiography alone in two (abrupt mid-systolic displacement or distinct U-shaped pansystolic posterior displacement of the leaflets[9,10]).

Systolic time intervals: All patients had simultaneous electrocardiographic, phonocardiographic and carotid arterial pulse tracings recorded photographically at paper speed of 100 mm/sec using an Electronics for Medicine VR-6 system. Systolic time intervals were measured as described previously.[1,2] The left ventricular ejection time (LVET) and preejection period (PEP) were corrected for heart rate with use of linear regression equations, and were expressed as their respective indexes (LVETI and PEPI).[1,2] The ratio of PEP/LVET was calculated using the uncorrected values for preejection period and left ventricular ejection time.

Echocardiography: An echocardiogram was recorded in all patients, with a Unirad series 100 echograph utilizing a 2.25 megahertz 0.5 inch (1.27 cm) transducer focused at either 5 or 7.5 cm, with a repetition rate of 1,000/hertz. The recordings were made on a Tektronix recorder. The transducer was usually held in the fourth intercostal space just to the left of the sternum, although occasionally it had to be placed in the third or fifth intercostal space to obtain resolution of the interventricular septum and left ventricular posterior wall endocardial echoes. Left ventricular minor axis dimensions were measured from recordings made with the ultrasonic beam so directed that the interventricular septum and the left ventricular posterior wall endocardium were clearly delineated in a position where the inferior mitral valve apparatus echoes (inferior edges of the leaflets or chordae tendineae) were evident. The left ventricular end-diastolic diameter (Dd) was measured from the endocardium of the interventricular septum to the endocardium of the posterior wall at the time of the

TABLE I

Summary of Clinical, Noninvasive and Hemodynamic Data

Case no.	Age (yr) & Sex	Grade (MR)	NYHA Class	Dig.	Etiology	%ΔD	Dd (mm)	PEPI (msec)	LVETI (msec)	PEP/ LVET	LVEDP (mm Hg)	PCW_m (mm Hg)	PA_m (mm Hg)
					Group I (%ΔD 30 percent or more)								
1	67M	III	III	Yes	PMV	42	63	131	381	0.39	11	12	22
2	40M	III	I	No	PMV	32	57	124	420	0.32	13	8	14
3	26M	III	I	No	PMV	39	50	130	379	0.40	4	5	9
4	22M	IV	II	No	Post IE	35	57	164	410	0.48	6	5	13
5	54M	III	II	Yes	RHD + RC	40	75	145	380	0.44	14	16	24
6	16F	IV	IV	Yes	RHD + RC	61	57	117	343	0.40	8	—	37
7	18F	II	II	No	PMV	38	47	134	395	0.38	5	4	13
8	46F	III	III	No	PMV	39	51	114	367	0.46	12	16	24
9	51M	III	III	Yes	PMV	49	68	137	391	0.41	18	25	36
10	61M	III	II	Yes	Post IE	34	47	140	391	0.40	18	23	33
11	63F	IV	III	Yes	PMD	34	58	150	407	0.43	0	5	20
12	48F	III	II	Yes	Unknown	36	59	174	380	0.48	14	15	19
13	40M	IV	III	Yes	Post IE	38	63	133	406	0.40	18	26	40
14	60F	III	III	Yes	PMV	46	52	163	395	0.46	11	8	12
15	52M	II	III	Yes	PMD	31	55	142	371	0.45	17	17	22
Mean						40	57	140	388	0.42	11.3	13	22.5
± SEM						±2.0	±2.0	±4.4	±5.0	±0.01	±1.4	±3.4	±2.6
					Group II (%ΔD less than 30 percent)								
16	64M	III	III	Yes	PMV	23	71	183	359	0.72	10	10	23
17	51M	III	IV	Yes	Unknown	27	51	145	369	0.53	15	30	63
18	45F	III	II	Yes	RHD + RC	26	70	186	370	0.68	16	14	32
19	49M	III	III	Yes	PMD	26	65	146	358	0.53	34	28	38
20	25F	III	III	Yes	RHD	29	58	163	369	0.67	7	15	16
21	63M	III	IV	Yes	PMV	19	63	191	374	0.64	11	13	23
22	69M	III	III	Yes	RHD	22	60	182	374	0.67	7	10	16
Mean						25	63	171	368	0.63	14.3	17.1	30.1
± SEM						±1.3	±2.7	±7.4	±2.5	±0.03	±3.5	±3.1	±6.2

Dd = left ventricular end-diastolic diameter; Dig. = maintenance digitalis therapy; LVEDP = left ventricular end-diastolic pressure; LVETI = left ventricular ejection time index; MR = mitral regurgitation; NYHA class = New York Heart Association functional class; PA_m = mean pulmonary arterial pressure; PCW_m = mean pulmonary wedge pressure; PEPI = preejection period index; PEP/LVET = ratio of preejection period to left ventricular ejection time; %ΔD = percent change in minor axis diameter; PMD = papillary muscle dysfunction due to coronary artery disease; PMV = prolapsed mitral valve; Post IE = postinfective endocarditis; RC = ruptured chordae tendineae; RHD = rheumatic heart disease; SEM = standard error of the mean.

TABLE II

Data in 25 Normal Subjects and 22 Patients With Mitral Regurgitation (mean ± standard error of the mean)

	Cases (no.)	%ΔD	Dd (mm)	PEPI (msec)	LVETI* (msec)	PEP/LVET
A. Normal	25	34 ± 0.4	46 ± 1.0	131 ± 2.1	405 ± 3.0	0.36 ± 0.007
B. Mitral regurgitation						
1. Group I (%ΔD≥30)	15	40 ± 2.0	57 ± 2.0	140 ± 4.4	388 ± 5.0	0.42 ± 0.01
2. Group II (%ΔD<30)	7	25 ± 1.3	63 ± 2.7	171 ± 7.4	368 ± 2.5	0.63 ± 0.03
P Value						
A vs. B_1		<0.001	<0.001	<0.05	<0.001	<0.001
A vs. B_2		<0.001	<0.001	<0.001	<0.001	<0.001
B_1 vs. B_2		<0.001	NS	<0.001	<0.01	<0.001

* Significance of data corrected for sex difference in groups.
NS = not significant; *P* = probability; other abbreviations as in Table I.

peak deflection of the QRS complex. The end-systolic diameter (Ds) was measured as the point of closest approximation of the interventricular septum and the posterior wall echoes in systole. The percent change in minor axis diameter (%ΔD) was calculated as Dd − Ds × 100/Dd. None of the patients had absent, atypical or paradoxical septal motion. The mean rate of circumferential shortening during ejection was not measured in this study because the motion of the left ventricular minor axis in mitral regurgitation begins before the onset of ejection.

The echocardiographically determined percent change of the left ventricular minor axis diameter (%ΔD) was used to classify the patients into two groups. The point of division was taken as %ΔD of 30 percent, which represents the lower limit of the normal distribution (2 standard deviations below the mean for normal subjects) in our laboratory. Group I consisted of 15 patients with a normal or increased %ΔD (30 percent or more). Group II consisted of 7 patients with a decreased %ΔD (less than 30 percent). Seventeen patients were receiving maintenance digitalis therapy. All five patients not receiving digitalis were in Group I.

Normal control group: Statistical comparisons were made with the aid of a Hewlett-Packard deskside computer (model 9810A). To validate the methodologic approach and the normal data range, 25 persons (10 female, 15 male) without cardiac disease were studied at the same time as the patients. The data in these normal subjects were within previously published norms for systolic time intervals[1,2] and echocardiographic measures.[4,11,12]

Cardiac catheterization: All patients underwent right and left cardiac catheterization within 7 days of the noninvasive studies. Cineangiograms of the left ventricle were obtained in the right anterior oblique view, and those of the ascending aorta in the left anterior oblique view. Selective coronary cineangiograms were obtained in the left and right anterior oblique views in all patients with use of either the Sones or Judkins technique. No patient demonstrated angiographic evidence of aortic valve disease. In the three patients found to have significant coronary artery disease (50 percent or greater narrowing of the luminal diameter of one or more coronary arteries), the mitral regurgitation was attributed to papillary muscle dysfunction. None of the other patients demonstrated narrowing of 50 percent or more in any artery. Because of the large size of the ventricle in most of the patients, angiographic imaging of the entire chamber could not be obtained in a single frame during diastole so that accurate ejection fraction measures were precluded.

The extent of mitral regurgitation was graded from the left ventricular cineangiocardiogram on a scale of I to IV. Grade I was defined as faint opacification of the left atrium during left ventricular systole that cleared completely during diastole; grade IV was defined as complete opacification of the left atrium during the first left ventricular systole; intermediate degrees were graded II or III. Two patients were found to have grade II mitral regurgitation; all others had grade III or IV.

Results

The clinical, noninvasive and hemodynamic data for the 22 patients are summarized in Table I. The average data for normal persons and the patients of Groups I (%ΔD 30 percent or more) and II (%ΔD less than 30 per cent) are summarized in Table II.

When compared with normal data, the mean preejection period index (PEPI) was prolonged and left ventricular ejection time (LVETI) was diminished in both groups of patients. The former index was longer and the latter more abbreviated in Group II than in

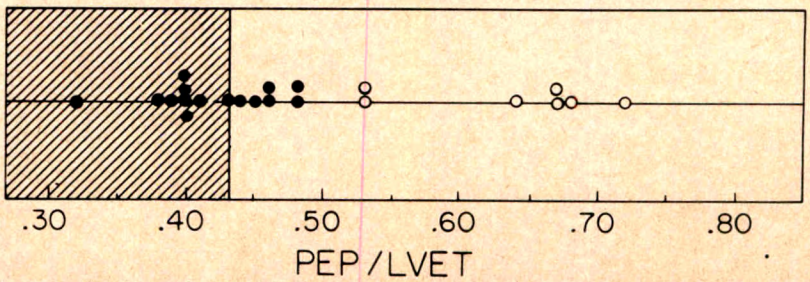


FIGURE 1. Distribution of ratio of preejection period and left ventricular ejection time (PEP/LVET) among patients with mitral regurgitation. **Solid circles** represent patients in Group I (percent change in minor axis diameter [%ΔD] 30 percent or more); **open circles** represent patients in Group II (%ΔD less than 30 percent).

Group I. The mean PEP/LVET ratio was increased in both groups and significantly greater in Group II than in Group I. The mean end-diastolic diameter (Dd) was increased in both groups. The difference in Dd between Groups I and II was not statistically significant. Seven of the 15 patients in Group I had a "supernormal" %ΔD (38 percent or more). Among these 7, the mean preejection period index and mean PEP/LVET ratio were increased whereas the mean left ventricular ejection time was decreased significantly ($P < 0.01$).

The distribution of the PEP/LVET ratio relative to % ΔD in the two groups is shown in Figure 1. PEP/LVET was less than 0.50 in all patients in Group I and greater than 0.50 in all patients in Group II. All patients with a normal PEP/LVET ratio had a normal or supernormal %ΔD.

The relation of PEP/LVET to % ΔD among all patients is illustrated in Figure 2 together with the range of 2 standard deviations for %ΔD and PEP/LVET for the 25 normal subjects. Previous studies[11] have shown an inverse relation between PEP/LVET and %ΔD in patients with coronary artery disease without mitral valve involvement.[11] Our patients with mitral regurgitation demonstrated an inverse relation between %ΔD and PEP/LVET; however, the range of their data was higher and to the right of that found among normal persons and in the previously studied patients without mitral valve disease. Thus, although the PEP/LVET ratio increased as %ΔD decreased in patients with mitral regurgitation, the PEP/LVET ratio for any level of %ΔD tended to be higher than that found in patients with isolated left ventricular disease. Among undigitalized patients with mitral regurgitation, the data were distributed in the same manner as for patients receiving maintenance digitalis therapy.

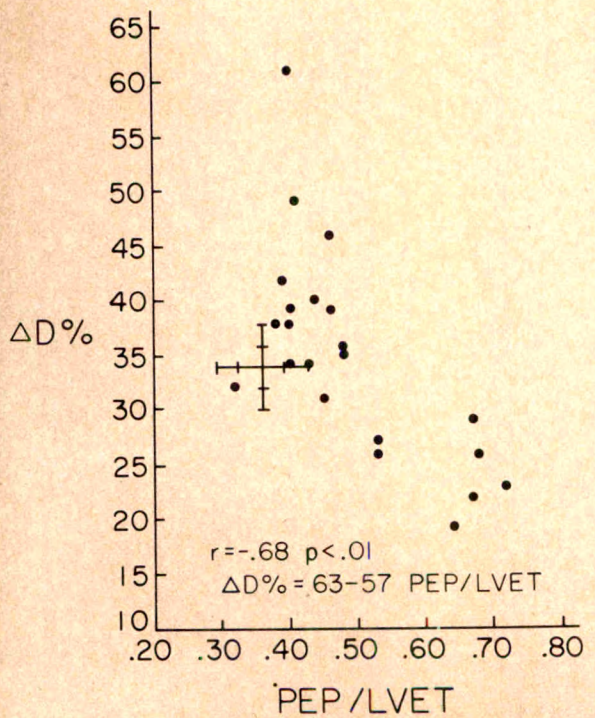


FIGURE 2 Relation of % ΔD to PEP/LVET ratio among 22 patients with mitral regurgitation. **Cross bars** represent mean ± 2 standard deviations for % ΔD and PEP/LVET among normal subjects.

The hemodynamic data (Table I) revealed no significant differences between the two groups of patients with mitral regurgitation in mean left ventricular end-diastolic pressure, mean pulmonary capillary wedge pressure or mean pulmonary arterial pressure. No close correlation between these hemodynamic measures and the echocardiographic and systolic interval data were observed.

Discussion

Systolic time intervals in patients with mitral regurgitation vary widely from normal to markedly abnormal. Interpretation of these data has been difficult because until now it has been impossible by noninvasive means to segregate the independent influence of mitral regurgitation from that due to diminished left ventricular contractile performance. Thus, prolongation of the preejection period and abbreviation of the left ventricular ejection time, with a consequent increase in PEP/LVET, may result from either the dynamic effects of mitral regurgitation or the influence of diminished intrinsic contractile performance of the left ventricle. The availability of echocardiographic methods for assessing the contractile performance of the left ventricular chamber, through measurement of changes in the excursion of the minor axis during systole, offers a new noninvasive approach to the analysis of left ventricular chamber performance in mitral regurgitation. Changes in the extent of motion of the diameter of the left ventricle have been shown to correlate well with overall left ventricular chamber performance assessed angiographically by measurement of the left ventricular ejection fraction in patients with cardiac valve disease.[4–7] It was on this basis that the percent change in minor axis diameter (%ΔD) was used to distinguish those patients with mitral regurgitation and good left ventricular function (%ΔD 30 percent or more) from those with diminished left ventricular performance (%ΔD less than 30 percent).

Relation of systolic time intervals and echocardiographic measurements: When compared with normal values, the mean preejection period index was lengthened, the mean left ventricular ejection time was abbreviated and the mean PEP/LVET ratio was increased among the patients with mitral regurgitation. When the patients were classified into those with normal or supernormal %ΔD (Group I) and those with diminished %ΔD (Group II), it became apparent that the latter had greater prolongation of the preejection period index and greater shortening of left ventricular ejection time and a greater increase in PEP/LVET. These group differences were associated with no significant difference in mean left ventricular end-diastolic diameter. Thus, when systolic performance is relatively well compensated in patients with mitral regurgitation, there is commonly a prolongation of the preejection period, abbreviation of the left ventricular ejection time and an increase in PEP/LVET. When mitral regurgitation is complicated by diminished left ventricular systolic performance, the changes in systolic intervals are accentuated and occur in virtually all patients. These

studies also suggest that the relation between systolic time intervals and left ventricular chamber performance as reflected in the measurement of change in minor axis diameter is relatively uninfluenced by digitalis administration.

It is important to recognize these relations in the interpretation of the systolic time intervals in patients with mitral regurgitation. Our data indicate that if PEP/LVET is greater than 0.5 in patients with mitral regurgitation there is a great probability that left ventricular performance is depressed. On the other hand, a normal PEP/LVET ratio in patients with isolated mitral regurgitation suggests that left ventricular performance probably is well compensated. It is to be noted that the range of systolic time intervals in the patients with mitral regurgitation reported herein are virtually the same as those observed in the studies by Kitchiner et al.,[13] wherein the systolic intervals were corrected for heart rate and the state of digitalization.

Factors influencing systolic time intervals: As noted previously, at least two factors influence the systolic time intervals in patients with severe mitral regurgitation: (1) the mechanical effect of a sustained degree of mitral regurgitation, and (2) the intrinsic performance of the left ventricular myocardium. It is probable that in the compensated left ventricle, the mechanical effect of mitral regurgitation (in which a significant portion of left ventricular volume is ejected into the left atrium during the preejection phase of systole) results in a diminished rate of left ventricular pressure development during the preejection period. As a result, the preejection component of systole is prolonged whereas the ejection phase is abbreviated commensurately. The shortening of left ventricular ejection time can be accounted for, in addition, by a diminished shortening capacity of the left ventricular fibers, since ventricular contraction begins before the onset of aortic ejection.[14] In addition to the mechanical effects of mitral regurgitation, alterations in contractile performance of the ventricle may diminish the rate of left ventricular force developed for any given ventricular systolic load. Such an alteration in contractile performance may result in further diminution in the rate of left ventricular pressure development, thus accentuating the prolongation of the preejection phase and the shortening of left ventricular ejection time.

Factors influencing echocardiographic measurements: The mean end-diastolic diameter of the left ventricle (Dd) was generally increased in the patients with mitral regurgitation, frequently in the presence of normal or only mildly elevated ventricular end-diastolic pressures. These data are consistent with previous observations demonstrating that the left ventricular end-diastolic volume may be increased in mitral regurgitation in the presence of normal or only slightly increased diastolic ventricular pressure.[15,16] Further, the increase in end-diastolic diameter was often associated with a normal or supernormal %ΔD. Thus, abnormal left ventricular performance cannot be recognized in mitral regurgitation solely on the basis of diastolic volume or pressure dimensions of the left ventricle, or both.

Clinical implication: The measurement of percent change in minor axis diameter of the left ventricle from the echocardiogram and the calculation of the PEP/LVET ratio from systolic time interval measurements provide an effective means of assessing overall left ventricular performance in patients with mitral regurgitation. The PEP/LVET ratio, which is often increased because of the mechanical effects of mitral regurgitation as such, remains a useful measure if it is recognized that the point of separation between normal and abnormal left ventricular chamber performance occurs at a higher level (0.50) than in patients without mitral valve disease. The finding of a normal PEP/LVET in patients with mitral regurgitation suggests that left ventricular performance is well preserved. The measurement of the diastolic diameter alone affords little aid in interpreting the changes in cardiac performance in patients with mitral regurgitation.

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Echocardiographic and Clinical Spectrum of Mitral Anular Calcification

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To establish the reliability of echocardiography in making the diagnosis of mitral anular calcification 10 consecutive patients with dense echoes at the mitral anular area were examined fluoroscopically, using an image intensifier. Nine of these had distinct mitral anular calcification. The echocardiographic reliability thus confirmed, 30 cases with similar findings were reviewed and the total group of 40 cases were used to define the echocardiographic spectrum of mitral anular calcification. This lesion extended variably from the anulus to involve the posterior left ventricular wall, mitral valve leaflets, aortic root, aortic valve and interventricular septum. The pleomorphic echocardiographic findings introduce difficulties in the diagnosis of pericardial effusion and mitral stenosis. Echocardiography is a reliable method of diagnosing mitral anular calcification, but care must be taken to avoid confusing this condition with others it resembles.

Calcification of the mitral valve anulus has been described both clinically and pathologically,[1–4] its antemortem identification depending on the radiologic presence of a C- or J-shaped density within the cardiac silhouette[1] (Fig. 1). We believe that the echocardiogram is now a sensitive tool for diagnosing this lesion. In this report we describe the extensive echocardiographic spectrum associated with calcification of the mitral anulus and review the clinical data of patients with this abnormality. We also touch on the diagnostic difficulties in the presence of mitral anular calcification.

Materials and Methods

There were two groups of patients: Group A, 10 patients studied prospectively, and Group B, 30 patients studied retrospectively.

Group A: A dense echo at the atrioventricular (A-V) junction, behind the anterior leaflet of the mitral valve and in front of the posterior ventricular endocardium, was considered evidence of mitral anular calcification. To validate this observation, 10 consecutive patients with this echocardiographic finding were evaluated prospectively by means of review of history, physical examination, phonocardiography, electrocardiography, and cardiac fluoroscopy with an image intensifier.

Group B: By virtue of the results obtained in Group A, we reviewed the echocardiograms of the 833 patients who underwent this study at this laboratory from October 1973 to August 1975. Thirty additional patients with echocardiographic stigmata of calcified mitral anulus were found. Because findings in the patients in group A and group B did not differ, all patients were considered homogeneous, and their charts were reviewed for pertinent clinical, roentgenographic and electrocardiographic data.

All echocardiograms were obtained with a Hoffrel 101C Ultra-Sonoscope, a Honeywell 1856 Visicorder, and a 2.25 megahertz 0.5 inch (1.27 cm) transducer focused at 7.5 or 10 cm. The standard longitudinal sweep technique of Feigenbaum[5] was used to record the echocardiogram in all patients. Phonocardiography was performed with an Irex 150 Continutrace multichannel recorder.

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Results

Echocardiographic Findings

The 10 patients in Group A were studied prospectively to validate that the abnormal echo at the A-V junction was due to calcification of the mitral anulus. Fluoroscopy of the heart with an image intensifier was used as the standard to compare the echocardiographic findings. Of the 10 patients, 9 had the typical fluoroscopic signs of anular calcification. This finding supported the hypothesis that the abnormal echo at the A-V junction is due to calcification of the mitralanulus. As mentioned, the 10 patients prospectively studied as well as 30 additional patients found by retrospective review of echocardiograms were then considered a single group. All 40 patients had an intense echo at the A-V junction behind the posterior aortic root-anterior mitral leaflet continuum (Fig. 2).

In 10 of the 40 patients the bright mitral anular echoes were generally localized to the area behind the posterior aortic root-anterior mitral leaflet continuum. A longitudinal sweep of the transducer demonstrated abrupt cephalad termination of the echoes at the A-V junction in seven of these patients and in the left atrium in the other three. When the transducer was directed caudally, the echoes faded into the echoes of the posterior left ventricular wall structures (Fig. 2).

Posterior left ventricular wall involvement: In 22 of the 40 patients, the bright mitral anular echoes maintained their intensity as the transducer was swept caudally into the left ventricular posterior wall structures, continuing for variable distances into the left ventricular chamber behind the posterior mitral leaflet before joining the posterior papillary muscle (Fig. 3). Eleven of these patients had associated calcification of the aortic valve and root. A discrete noncalcified or nonthickened posterior mitral leaflet could be separately identified in 5 of these 22 patients with posterior wall involvement. This leaflet remained adjacent to the mitral anulus and the posterior left ventricular wall with

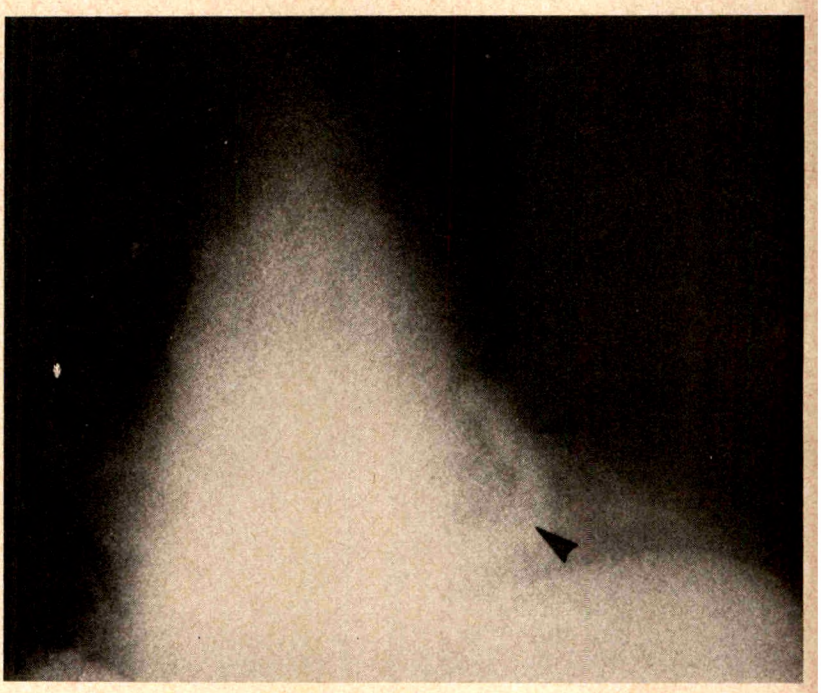


FIGURE 1. Chest X-ray film (overexposed) demonstrating the J-shaped density **(arrow)** within the cardiac silhouette.

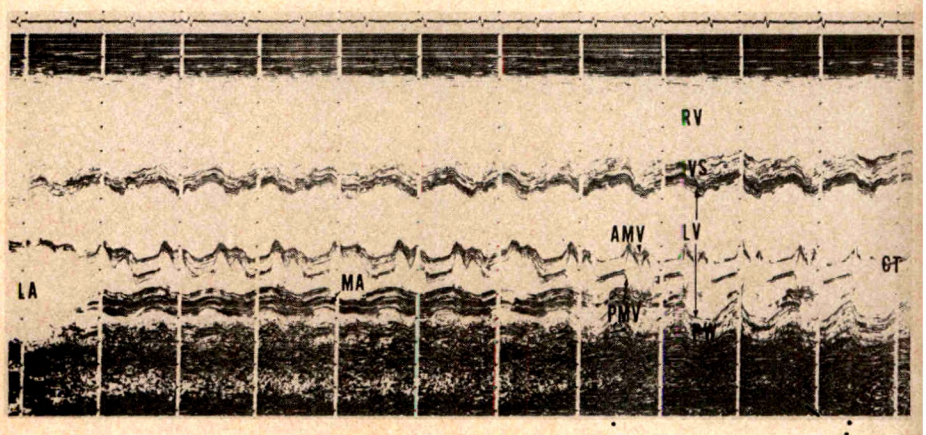


FIGURE 2. M mode echocardiogram showing mitral anular calcification. Calcification is restricted to the base of the left ventricle at the atrioventricular junction. Distinct noncalcified structures can be identified as the transducer is swept from the left atrium toward the apex of the left ventricle. AMV = anterior mitral valve leaflet; CT = chordae tendineae; IVS = interventricular septum; LA = left atrial cavity; LV = left ventricular cavity; MA = mitral anulus; PMV = posterior mitral valve leaflet; PW = posterior left ventricular wall; RV = right ventricular cavity. Time lines = 1 second. Stroboscopic dots = 1 cm tissue depth. Electrocardiogram is on top.

a reduction of the amplitude of the posterior mitral leaflet motion (Fig. 3). On the other hand, a discrete posterior mitral leaflet could not be identified in the 17 remaining patients, since all the posterior wall structures formed an inseparable mass of echoes extending from the mitral anulus toward the apex of the left ventricle (Fig. 4).

The motion of the thickened and calcified mitral anulus generally paralleled that of the left ventricular posterior wall and aortic root. Initial systolic posterior movement coincidental with isovolumetric contraction of the left ventricle was followed by anterior motion that reached its apex simultaneously with the maximal excursion of the posterior left ventricular wall (Fig. 4).

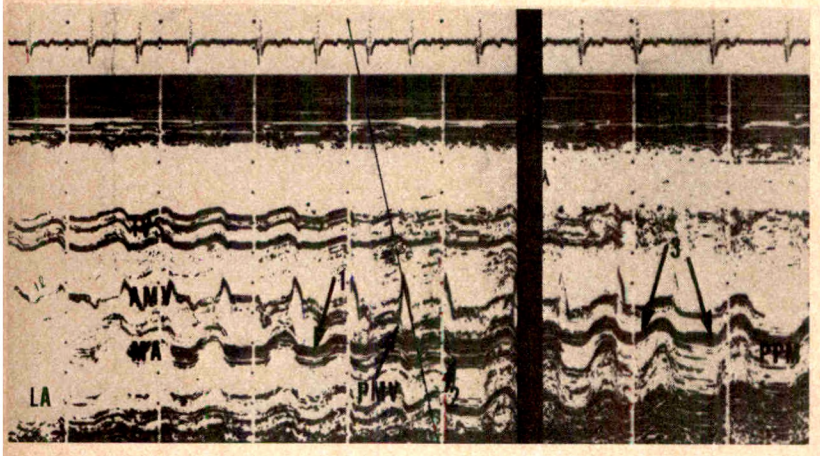


FIGURE 3. The anular calcification extends from the mitral anulus (MA) into the left ventricle. Discrete structures in the left ventricle can still be identified. The mitral anular calcification begins abruptly at the atrioventricular junction **(arrow 1).** A distinct posterior mitral leaflet (PMV) can be identified with a thick mass of calcification behind it **(arrow 2).** The calcification extends into the region of the posterior papillary muscle (PPM) **(arrow 3).** Electrocardiogram is on top. Abbreviations as in Figure 2.

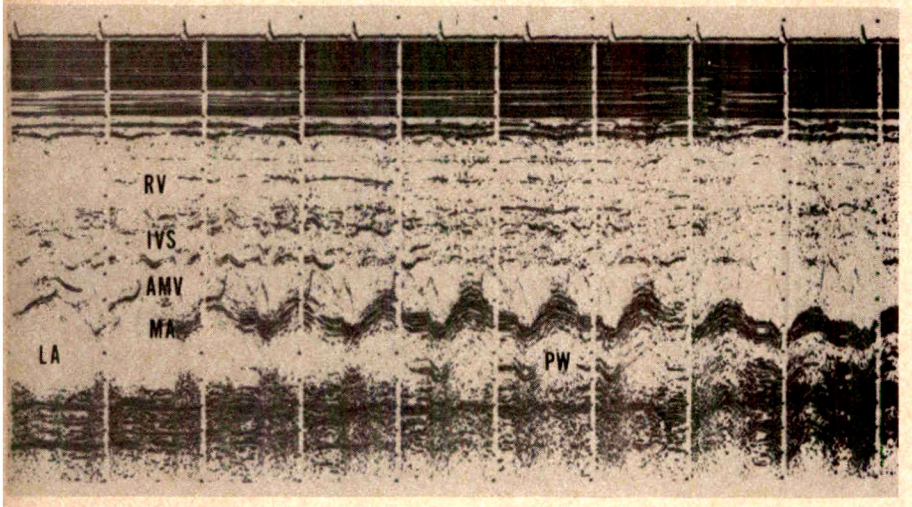


FIGURE 4. The anular calcification begins abruptly in the left atrium (LA) and extends into the posterior wall (PW) of the left ventricle. Identification of the posterior mitral leaflet, left ventricular endocardium, chordae tendineae and posterior papillary muscle is obscured. Abbreviations as in Figure 2.

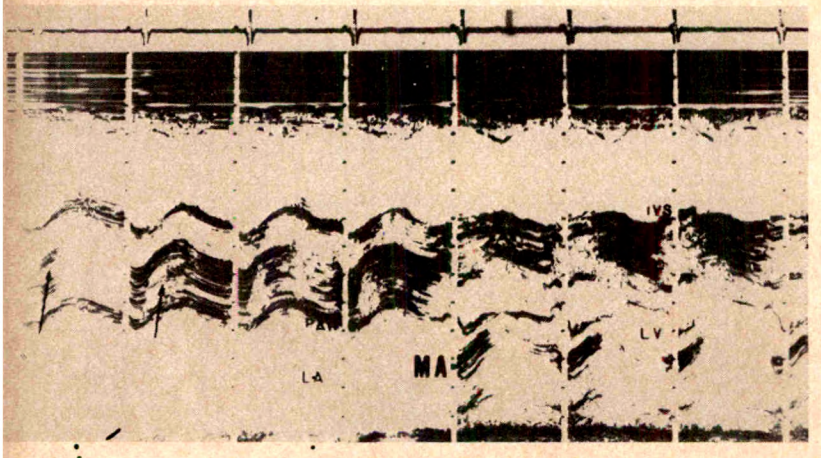


FIGURE 5. The mitral anular calcification ends at the atrioventricular junction. Calcification of the aortic root, aortic leaflets **(arrows)** and interventricular septum (IVS) is not continuous with the mitral anulus (MA) in this sweep. PAW = posterior aortic wall.

When the early systolic posterior notch was absent, which it occasionally was, the mitral anular movement resembled a sine wave (Fig. 3). In patients with a small left ventricular chamber, the systolic excursion of the mitral anulus impinged on the mitral valve leaflets and appeared to thrust them anteriorly, toward and against the interventricular septum, thereby narrowing the echocardiographic appearance of the left ventricular outflow tract (Fig. 4).

Involvement of aortic structures: In the remaining eight patients the extent of the calcification was limited to the mitral anulus and aortic structures. This gave a total of 19 patients who had thickening and calcification of the aortic structures in addition to the mitral anulus. Continuity of the intense echoes from the mitral anulus to the aortic leaflets or root could be demonstrated in only five patients (Fig. 5 and 6). The patients with calcification of the aortic valves showed a significant average reduction in the maximal systolic opening of this valve (8.6 ± 5.3 mm standard deviation) when compared with those patients who had no calcification of the aortic valve (14 ± 3.3 mm standard deviation) ($P < 0.005$). Ten of the 17 patients had a maximal opening of less than 10 mm, which meets the echocardiographic criterion for aortic valve stenosis.

Involvement of mitral leaflets: The diastolic closing slope of the anterior mitral valve leaflet (E-F slope) showed great variation, ranging from 10 to 150 (average 63) mm/sec. Four patients had calcification of the anterior leaflet of the mitral valve. In four of the eight patients who demonstrated an E-F slope of 35 mm/sec or less, the E point of the anterior mitral leaflet impinged on the interventricular septum and remained against it during the initial portion of diastole. Three of these four patients also had concentric hypertrophy of the left ventricle with a small internal diastolic dimension. These four patients had no thickening or reduplication of the anterior mitral leaflet and they did

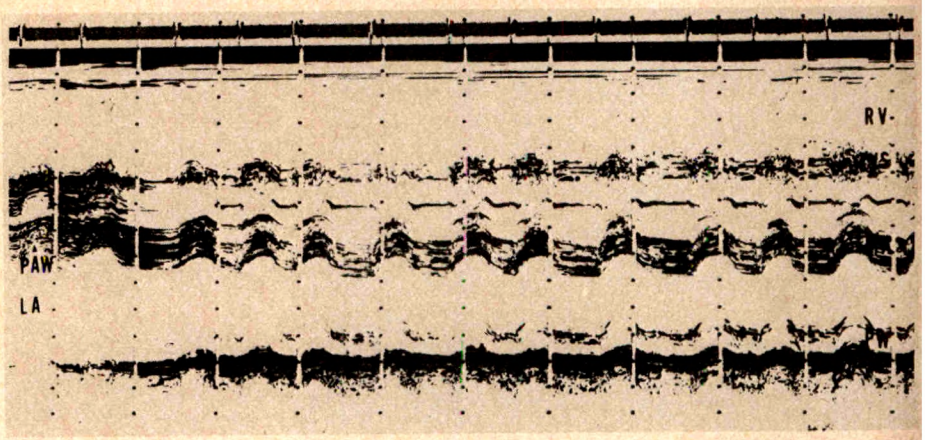


FIGURE 6. Calcification of the mitral anulus (MA) extending into the posterior aortic wall (PAW). This sweep demonstrates continuity of the calcification.

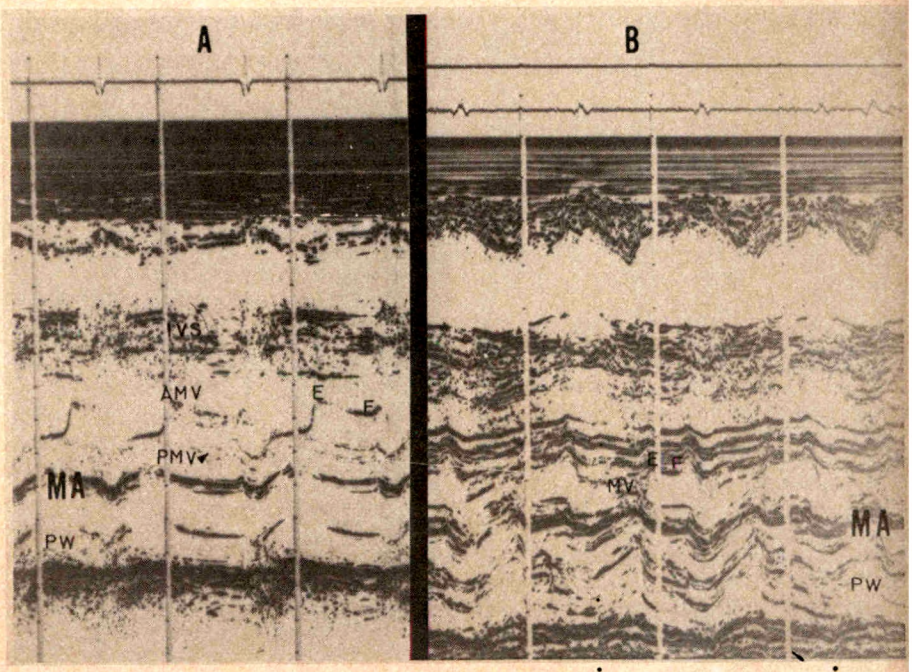


FIGURE 7. Echocardiograms demonstrating reduction in E-F slope. **A,** the E-F slope is markedly reduced but the anterior mitral valve leaflet (AMV) is not thickened. The posterior mitral valve leaflet (PMV) moves slightly posteriorly in early diastole, paralleling the motion of the calcified mitral anulus (MA). **B,** the E-F slope is reduced and the mitral valve seems to be encased by a calcified anulus posteriorly and possibly calcified chordae tendineae anteriorly. The posterior leaflet has a distinct posterior excursion in early diastole.

not meet other echocardiographic criteria for mitral stenosis (Fig. 7). The other four patients with a greatly reduced E-F slope, thickening and reduplication of the anterior mitral leaflet better met the general criteria for mitral stenosis. However, the posterior mitral valve leaflet did not move anteriorly in diastole in any of the patients, despite the reduction of the E-F slope and reduplication of the anterior mitral leaflet. Only one patient was thought to have mitral stenosis clinically. There was also calcification of the anterior mitral leaflet in one patient who had a normal E-F slope.

Left ventricular dimensions: Although the cardiothoracic ratio was enlarged on chest X-ray film in 31 patients, the left ventricular internal diameter, as measured with echocardiography, was enlarged in only 11 patients (58 mm or more). The left ventricular wall and interventricular septal thickness were enlarged in more than half of the cases, suggesting concentric hypertrophy of the left ventricle without undue dilatation.

Clinical Data

The average age of the group of 40 patients was 73 years (range 50 to 89 years). There were 32 women and eight men.

Cardiac murmurs: The patients had various diagnoses including coronary artery disease (13), hypertensive cardiovascular disease (7), aortic stenosis (6), both valvular and subvalvular, mitral insufficiency (5), aortic insufficiency (1), combined cardiac valve disease (3), alcoholic cardiomyopathy (1), uremia (1) and various disorders of rhythm (26). However, because most patients were referred to the echocardiographic laboratory for evaluation of systolic murmurs, there was a built-in bias, resulting in an extremely large incidence of systolic murmurs (35). These were varied in location, radiation, character and duration (Fig. 8). Most patients had a harsh, nonholosystolic or systolic ejection murmur at the apex or the right sternal border at the second intercostal space or the left sternal border at the fourth intercostal space. Five patients had an apical holosystolic murmur, whereas 12 had more than one systolic murmur. Eight of the 10 patients with reduced aortic valve motion had a systolic ejection murmur along the right sternal border at the second intercostal space. Five patients had a diastolic murmur.

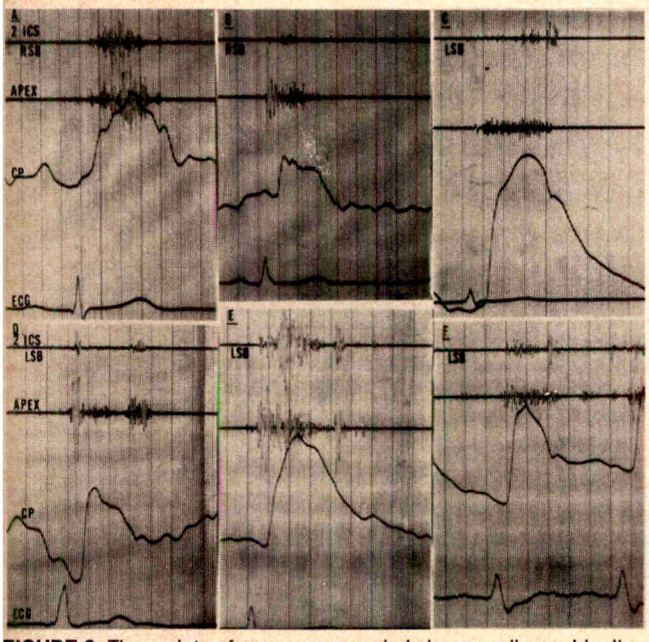


FIGURE 8. The variety of murmurs recorded phonocardiographically. **A,** there are systolic ejection murmurs at the apex and aortic area. The carotid pulse (CP) tracing shows evidence of aortic valve stenosis. **B,** a decrescendo systolic murmur at the apex. **C,** a holosystolic murmur at the apex. **D,** a systolic murmur with an early crescendo-decrescendo configuration and a late crescendo component at the apex. **E,** a systolic ejection murmur at the apex and base, and a diastolic decrescendo murmur at the apex. The carotid pulse suggests aortic valve stenosis. **F,** a holosystolic murmur at the apex, which is transmitted to the base. The apical murmur seems to extend into the transmitted pulmonary closure sound. Thus it is possibly an early diastolic murmur. ECG = electrocardiogram; LSB = left sternal border; RSB = right sternal border; 2 ICS = second intercostal space.

Radiologic findings: The chest X-ray films were reviewed by an independent observer who noted calcification of the mitral anulus in 13 cases. Notably, of the 10 patients who manifested calcification of the mitral anulus on fluoroscopy (9 in group A and 1 in group B), only 5 had evidence of calcification in the routine chest X-ray film. Cardiomegaly was present in 31 patients.

Electrocardiographic findings: Most patients had an abnormal electrocardiogram demonstrating myocardial infarction (13), left ventricular hypertrophy (13), atrial fibrillation (13) or conduction defects (14). Of the 14 patients with conduction defects, 10 had first degree A-V block, 4 had left bundle branch block, 6 had left anterior hemiblock and 2 had both left anterior hemiblock and right bundle branch block.

Discussion

Mitral anular calcification has been described extensively in pathologic studies and in several clinical reports.[1–3] In addition to cardiac fluoroscopy, echocardiography appears to be a sensitive technique for diagnosing this condition. The clinical significance of the lesion depends in part on the extent of functional interference of the mitral valve, associated valvular aortic stenosis, idiopathic hypertrophic subaortic stenosis and involvement of the conduction system. However, the echocardiographic significance encompasses a wider spectrum, for this lesion may simulate other types of heart disease. The patient with calcification of the mitral anulus also frequently has a murmur that suggests valvular or subvalvular aortic stenosis or mitral insufficiency. The echocardiogram may differentiate between these lesions or demonstrate that more than one lesion is present.

Comparison of pathologic and echocardiographic findings: Pathologic study of mitral anular calcification[3] locates most deposits of calcium in the posterior portion of the anulus, which may extend into the left atrium and into the left ventricle behind the mitral valve leaflets. The deposits of calcium may be 1 to 3 cm in diameter and project as far as 3.5 cm into the adjacent myocardium. The interventricular septum is usually less

severely involved. Korn et al[3] noted calcium deposits in the anterior mitral leaflet, but not in the posterior leaflet. However, there was thickening of both leaflets with some commissural adherence of the leaflets where they underlay the anulus. In particular, the posterior leaflet was raised by the calcium deposit, thus causing interference with valve function. Fertman and Wolff[1] using a more sensitive technique described three patients who had extension of the anular calcification into both leaflets.

Data from the autopsy studies and our echocardiographic studies compare favorably with reference to the location and extent of calcification in the mitral anulus[1–3] because the densest echoes come from the posterior portion of the mitral anulus and frequently extend into the left ventricular apex. The posterior mitral leaflet does have its motion restricted, and is often drawn tightly against the calcium deposits of the anulus so that it is not visualized as a separate structure. In systole both leaflets are occasionally pushed forward by the massive deposits of calcium, perhaps compromising the size of the left ventricular outflow tract.

The pathologic studies as well as our studies demonstrate calcification of the aortic leaflets. The higher incidence rate of aortic calcification (48 percent) in our patients probably represents the greater sensitivity of the echocardiogram in detecting calcification. The degree of aortic stenosis has not been mentioned previously. Our demonstration of decreased maximal opening of the aortic valve when that valve is calcified suggests that calcific aortic stenosis and calcification of the mitral anulus are related. This view is further supported by studies demonstrating that the calcification is of the same histologic type in both lesions[1–3] and probably represents a similar degenerative process.

In one patient in group A anular calcification was not evident on fluoroscopic examination. A possible explanation may be that echocardiography is a more sensitive technique than fluoroscopy. Alternatively, the dense echoes from the mitral anulus, posterior mitral leaflet, chordae tendineae and posterior papillary muscle may in some instances represent fibrous thickening rather than calcification.

Associated cardiac diseases: Our patients had various cardiovascular diseases, as expected in an elderly group of patients. These diseases are not necessarily related to anular calcification. Coronary heart disease and hypertensive cardiovascular disease, as in previous reports, were most prevalent. Associated mitral insufficiency could not be fully assessed because an apical murmur or cardiac enlargement does not necessarily indicate the extent of mitral insufficiency in this type of patient and cardiac catheterization studies were rarely performed. The frequency of calcific aortic stenosis associated with anular calcification suggests the similarity of the underlying degenerative process. The large incidence of conduction disturbances is striking. Age is a factor and may have its effect through the process of degenerative calcification extending from the anterior anulus into the interventricular septum involving the conduction system.

Differentiation from pericardial effusion: The possibility of confusing mitral anular calcification with pericardial effusion has recently been reported.[6] This may occur when the anular echo is mistaken for the epicardium. The endocardial echo is frequently of low intensity and overlooked, which allows the space between the anulus and true epicardium to appear echo-free. Several of our cases had this appearance. The distinction between this configuration and a true pericardial effusion could usually be made by following the anular echo to its abrupt cephalad termination. The epicardial echo of a true effusion does not end abruptly but joins the pericardium at the left atrial wall. We have noted a patient (not in this series) whose calcified mitral anulus extended to the posterior left atrial wall, thus making the distinction between pericardial effusion and anular calcification even more difficult (Fig. 9).

Associated mitral stenosis and its echocardiographic diagnosis: The association of mitral stenosis with anular calcification has been appreciated by several

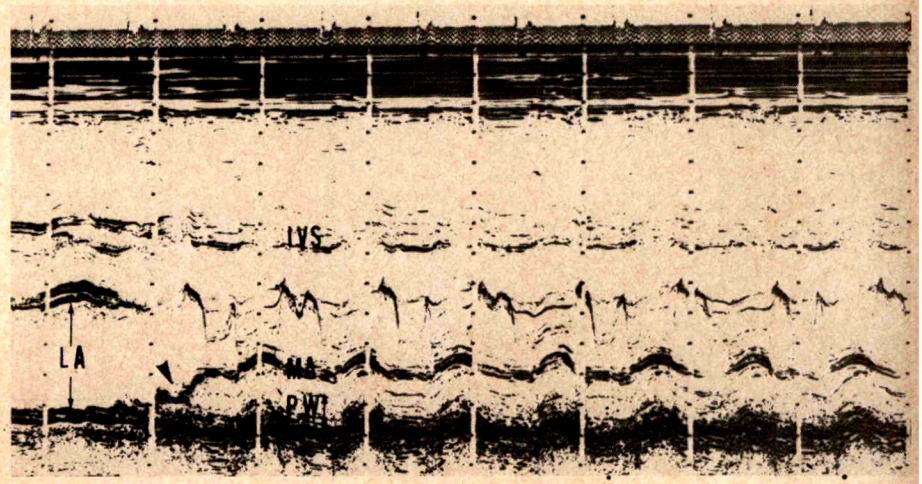


FIGURE 9. Calcified mitral anulus mimicking a pericardial effusion. The clear space behind the calcified mitral anulus (MA) may be mistaken for a pericardial effusion. The anular calcification extends to the left atrial wall **(arrow).** LA = left atrial cavity; PW = posterior left ventricular wall.

pathologists. The incidence is considerable; Korn et al.[3] found significant stenosis in 9 of 14, and slight stenosis in the remaining 5 patients with anular calcification. The echocardiographic diagnosis of mitral stenosis in these patients presents more of a problem. Reduction of the E-F slope alone is a notoriously poor criterion,[5] and assumes diagnostic qualities only when allied with thickening and reduplication of the anterior mitral leaflet. The diagnosis is further enhanced if the posterior leaflet moves anteriorly in diastole, or at least has a reduced posterior diastolic excursion. The nature of the anular lesion predisposes to all these features to some extent. The E-F slope is reduced frequently by multiple factors in this elderly group of patients. They had a reduced diastolic left ventricular compliance, and the valve leaflets may be calcified. The excursion of the posterior mitral leaflet may also be reduced by the distortion of the calcium mass behind it or by fusion with this mass. Indeed, as Korn et al.[3] suggested, all these patients may have a degree of mitral stenosis and many may have significant obstruction to flow. In our series, only one patient fulfilled rigid echocardiographic criteria for mitral stenosis and he had a mixed mitral lesion clinically. Clinical findings of mitral stenosis were absent in the patients with a severely reduced E-F slope. Careless interpretation of these echocardiograms may lead to the erroneous diagnosis of mitral stenosis in patients with anular calcification. The true association of mitral stenosis with anular calcification will probably remain obscure because these elderly patients are not candidates for casual cardiac catheterization, particularly in their relatively asymptomatic state.

Clinical implications: The echocardiogram can be used to diagnose calcification of the mitral anulus. In patients with this condition it can help the clinician to account for systolic murmurs, find or exclude associated valve lesions and provide a rationale for conduction defects. The echocardiogram also permits partial assessment of associated disorganized wall motion and ventricular hypertrophy and dilation in elderly or ill patients. It allows a sophisticated approach in selecting therapy or more invasive investigations. The echocardiographic lesion of calcified mitral anulus must be distinguished from pericardial effusion in order to avoid harming the patient with inappropriate therapy for a lesion that does not exist.

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Favorable Effects of Oral Maintenance Digoxin Therapy on Left Ventricular Performance in Normal Subjects: Echocardiographic Study

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Left ventricular performance was assessed with echocardiography in 10 normal subjects before and during maintenance therapy with digoxin (0.5 mg/day orally) in the basal state and after acute pressure loading with intravenously administered phenylephrine. During digoxin therapy, despite a decrease in mean heart rate of 5 beats/min in the basal state, mean left ventricular ejection fraction increased from 74 ± 2 to 79 ± 1 percent (standard error, $P < 0.03$); percent shortening of a left ventricular minor dimension increased from 37 ± 2 to 41 ± 1 percent ($P < 0.04$) and the mean rate of left ventricular dimension shortening increased from 5.66 ± 0.22 to 6.31 ± 0.23 cm/sec ($P = 0.05$). During acute pressure loading with phenylephrine there was no change in mean heart rate after digoxin and mean ejection fraction increased from 69 ± 3 to 75 ± 2 percent; mean percent shortening increased from 33 ± 2 to 38 ± 2 percent; mean rate of shortening increased from 5.46 ± 0.32 to 6.48 ± 0.33 cm/sec and mean normalized rate of shortening increased from 1.11 ± 0.06 to 1.29 ± 0.05 sec^{-1} (all $P < 0.01$). In a few subjects the response to digoxin did not coincide with the mean data for the whole group. This variability was largely due to difficulties in exactly matching heart rate between the control and digoxin studies. These data (1) support the concept that long-term oral digoxin therapy exerts a positive inotropic effect on the normal left ventricle, and (2) demonstrate the usefulness of echocardiography in noninvasive assessment of the effects of drugs on left ventricular performance.

There is little information concerning the effects of maintenance oral digoxin therapy in normal human subjects because of the need for a noninvasive technique for directly evaluating left ventricular performance. The echocardiographic assessment of left ventricular ejection phase indexes has been shown to correlate well with the cineangiographic determination of the same measures.[1,2] These indexes are known to be influenced by changes in heart rate and blood pressure,[3] but not by alterations in left ventricular end-diastolic volume.[4] Thus, if heart rate and blood pressure are controlled, these echocardiographic measures should be useful for assessing changes in left ventricular performance induced by cardioactive drugs. For these reasons, we designed a protocol to study the effects of maintenance oral digoxin therapy on echocardiographic indexes of left ventricular performance in normal human subjects at rest and during acute pressure overloading.

Methods

Subjects and Procedure

The study group consisted of 10 normal volunteers, 5 women and 5 men, aged 21 to 29 years. On their initial visit a complete history, physical examination, serum creatinine determination, electrocardiogram and echocardiogram were

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obtained. If these were normal, the study procedures and potential risks were described in detail, and the subjects signed an informed consent form approved by the University of California at San Diego Human Subjects Committee.

On another day with the subject in the supine position an intravenous infusion of 5 percent dextrose and water was begun. Blood pressure was measured by cuff sphygmomanometer and a control echocardiogram was obtained. Heart rate was calculated from the simultaneously recorded electrocardiogram. After the heart rate response to increased arterial pressure was prevented by the administration of atropine (1 to 1.5 mg intravenously), a solution of phenylephrine (40 mg/liter) was infused over 5 to 10 minutes in a quantity sufficient to increase the systolic arterial pressure approximately 40 mm Hg. While pressure was maintained at this level, another echocardiogram was obtained and the infusion was terminated. The total volume of fluid administered throughout the entire study did not exceed 50 ml.

After the control measurements were obtained, each subject took digoxin, 0.5 mg daily for 10 to 14 days. Eight to 12 hours after the last dose of digoxin echocardiograms were again obtained in the basal and pressure-loaded state as described. At the same time, serum levels of digoxin were measured.[5] All the digoxin levels were within the therapeutic range (mean 1.1 ng/ml; 0.7 to 1.9 ng/ml), and no subject reported side effects associated with administration of digoxin.

Echocardiography

Echocardiograms were recorded with a Picker Ultrasonoscope utilizing a 2.5 megahertz transducer focused at 7.5 cm. Recordings were made on a Honeywell Visicorder, model 1856, at a paper speed of 100 mm/sec. The electrocardiogram and the indirect carotid arterial pulse tracing were simultaneously recorded in each patient. The "standard intercostal space" technique was employed to obtain reproducible echocardiograms of the endocardial surface of the left ventricle at the level of the chordae tendineae.[6] The left ventricular end-diastolic dimension (EDD) was measured as the distance between the endocardial surface of the left side of the interventricular septum and the posterior wall at the peak of the R wave of the simultaneously recorded electrocardiogram. The end-systolic dimension (ESD) was measured as the smallest distance between these two surfaces even if the point of maximal excursion of each wall was not exactly opposed. Left ventricular ejection time (ET) was obtained from the simultaneously recorded indirect carotid pulse tracing. Utilizing these measurements the following calculations were made:

Percent of the left ventricular volume ejected per beat (EF) =

$$EF = \frac{EDD^3 - ESD^3}{EDD^3} \times 100 \text{ percent} \quad [1]$$

Percent shortening of the left ventricular dimension (ΔD) =

$$\Delta D = \frac{EDD - ESD}{EDD} \times 100 \text{ percent} \quad [2]$$

Rate of left ventricular dimension shortening (DV) =

$$DV = \frac{EDD - ESD}{ET} \quad [3]$$

TABLE I

Effect of Maintenance Oral Digoxin Therapy on Various Hemodynamic Measures in the Basal State and During Acute Pressure Overloading with Phenylephrine

Case no.	State	Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)		EF (%)		ΔD (%)		DV		V_d	
		Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin
1	B	69	63	112	98	76	84	38	46	5.39	7.12	1.16	1.42
	P	99	102	152	150	73	77	35	38	6.00	8.00	1.26	1.34
2	B	75	65	108	118	60	76	26	38	4.64	6.60	0.94	1.34
	P	82	83	150	150	53	69	22	33	4.21	5.90	0.80	1.14
3	B	54	55	100	120	74	79	37	40	6.14	6.69	1.11	1.22
	P	93	95	150	158	70	79	33	40	6.19	7.41	1.12	1.39
4	B	63	62	107	108	78	78	40	39	6.5	5.62	1.23	1.21
	P	74	78	150	170	74	78	36	40	5.93	6.75	1.14	1.27
5	B	70	54	92	90	67	78	35	40	4.98	5.34	1.14	1.21
	P	88	87	148	144	62	77	28	39	4.25	6.06	0.98	1.37
6	B	73	66	108	116	82	78	44	40	5.94	5.74	1.37	1.24
	P	112	106	170	165	83	83	44	45	6.99	7.34	1.47	1.48
7	B	66	62	108	104	75	79	37	41	5.88	6.15	1.23	1.33
	P	110	101	150	150	63	62	28	28	4.38	4.32	1.00	0.92
8	B	81	82	104	105	69	74	33	37	4.73	5.54	1.07	1.29
	P	92	124	148	150	67	74	31	36	4.67	6.45	1.02	1.41
9	B	64	64	120	128	79	78	41	40	6.48	6.65	1.25	1.30
	P	104	94	158	158	74	73	36	35	6.32	5.79	1.21	1.18
10	B	57	46	106	118	81	86	43	49	5.95	7.55	1.32	1.54
	P	67	95	158	160	75	82	37	43	5.64	6.81	1.14	1.40
Mean	B	67	62	107	111	74	79	37	41	5.66	6.31	1.24	1.31
SE		3	3	3	4	2	1	2	1	0.22	0.23	0.06	0.03
P		<0.02		NS		<0.03		<0.04		=0.05		NS	
Mean	P	93	97	153	156	69	75	33	38	5.46	6.48	1.11	1.29
SE		5	4	2	3	3	2	2	2	0.32	0.33	0.06	0.05
P		NS		NS		<0.01		<0.01		<0.01		<0.01	

B = basal; ΔD = percent shortening of the left ventricular dimension; DV = rate of left ventricular dimension shortening; EF = percent of the left ventricular volume ejected per beat; NS = not significant; P = during pressure overloading; *P* = probability; SE = standard error; V_d = normalized rate of left ventricular dimension shortening.

Normalized rate of left ventricular dimension shortening =

$$V_d = \frac{EDD - ESD}{EDD \times ET} \quad [4]$$

All data were analysed by the paired Student's t test comparing the control measures to the digoxin measures in each subject in the basal state and during acute pressure loading. Thus, each subject served as his or her own control.

Results

Group data (Table I): *In the basal state,* the mean resting heart rate decreased with digoxin from 67 ± 3 to 62 ± 3 (mean ± standard error) beats/min (P <0.02). However, mean systolic arterial pressure was not altered significantly. Despite this decrease in heart rate, mean ejection fraction increased significantly during digoxin administration (from 74 ± 2 to 79 ± 1 percent; P <0.03) as did mean percent shortening of left ventricular dimension (from 37 ± 2 to 41 ± 1 percent; P <0.04) and mean rate of shortening (from 5.66 ± 0.22 to 6.31 ± 0.23 cm/sec; P = 0.05). The mean normalized rate of shortening was also increased with digoxin, but this change did not achieve statistical significance in the basal state. The mean end-systolic dimension decreased from 3.01 ± 0.12 to 2.83 ± 0.08 cm (P = 0.05), but there was no change in end-diastolic dimension or ejection time.

During infusion of phenylephrine, mean heart rate and mean systolic arterial pressure were not significantly different between the control and digoxin measurements. Mean ejection fraction increased significantly after digoxin (from 69 ± 3 to 75 ± 2 percent; P <0.01) as did mean percent shortening of left ventricular dimension (from 33 ± 2 to 38 ± 2 percent; P <0.01), mean rate of shortening (from 5.46 ± 0.32 to 6.48 ± 0.33 cm/sec; P <0.01) and mean normalized rate of shortening (from 1.11 ± 0.06 to 1.29 ± 0.05 sec^{-1}; P < 0.01). The mean end-systolic dimension decreased from 3.28 ± 0.12 to 3.12 ± 0.11 cm, but this change did not achieve statistical significance. There was no change in end-diastolic dimension or ejection time after digoxin. An example of the increase in left ventricular performance during digoxin therapy and acute pressure loading in Subject 2 is shown in Figure 1.

Individual data (Table I): *In the basal state,* 7 of the 10 subjects had a consistent improvement in all four ejection phase indexes of left ventricular performance during digoxin therapy. Subject 9 had improvement in the rate of left ventricular shortening and the normalized rate only, and Subjects 6 and 4 showed no improvement.

During acute pressure loading 7 of the 10 subjects showed consistent improvement in all four measures while receiving digoxin. Subject 6 demonstrated improvement in the rate of shortening only, and Subjects 7 and 9 showed no improvement. However, these three were the only subjects whose heart rate after digoxin therapy was 6 or more beats/min lower during acute pressure loading than in the control state.

Reproducibility studies (Table II): Subjects 2 and 3, whose four ejection phase indexes were consistently improved by digoxin therapy, repeated the study to assess any variability in the response of individual subjects studied at different times. Both again showed increased left ventricular performance during digoxin therapy in the pressure-loaded state. In the basal state Subject 2 again showed improvement, but Subject 3 did not. However, during the repeat study the heart rate of Subject 3 was 45 beats/min during digoxin therapy, which was considerably below both the repeat control value of 53 beats/min and the basal heart rate of 55 beats/min during digoxin therapy in the first study.

Subject 7 also repeated the study to delineate further the importance of accurately matching heart rate in the control and digoxin studies during acute pressure loading. In the first study, she did not demonstrate improved left ventricular performance with pressure loading during digoxin therapy, but her heart rate was 9 beats/min less than the control value at the same blood pressure. During the second study, heart rate was

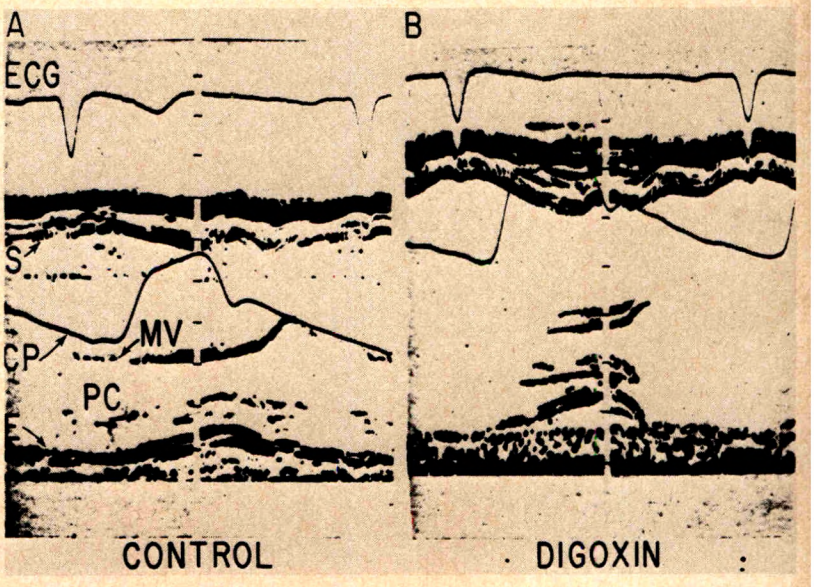


FIGURE 1. Subject 2. **A,** Control echocardiogram during acute pressure loading with phenylephrine in the first study obtained in this subject. Heart rate = 82 beats/min, systolic blood pressure = 150 mm Hg, ejection fraction = 53 percent, percent shortening of left ventricular dimension = 22 percent, rate of shortening = 4.21 cm/sec and normalized rate of shortening = 0.80 sec^{-1}. **B,** Echocardiogram during digoxin therapy and acute pressure loading. Considerable improvement in left ventricular performance is demonstrated. Heart rate = 83 beats/min, systolic blood pressure = 150 mm Hg, ejection fraction = 69 percent, percent shortening = 33 percent, rate of shortening = 5.9 cm/sec and normalized rate of shortening = 1.14 sec^{-1}. CP = indirect carotid pulse tracing; E = posterior left ventricular wall endocardium; ECG = electrocardiogram; MV = anterior mitral valve leaflet; PC = posterior mitral valve leaflet chordae tendineae; S = interventricular septum.

TABLE II

Repeat Studies in Three Subjects

Case no.	State	Heart Rate (beats/min)		Systolic Blood Pressure (mm Hg)		EF (%)		ΔD (%)		DV		V_d	
		Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin	Control	Digoxin
2	B	63	55	100	106	64	78	29	40	5.30	7.00	1.01	1.28
	P	98	86	144	149	67	73	31	35	5.98	6.50	1.17	1.21
3	B	53	45	106	116	82	77	44	39	7.21	6.25	1.27	1.18
	P	107	89	162	158	71	78	34	40	5.89	7.05	1.13	1.33
7	B	66	65	108	106	73	73	36	35	5.51	5.46	1.10	1.20
	P	107	103	150	149	69	73	32	36	5.93	5.95	1.15	1.25

Abbreviations as in Table I.

better matched (difference 4 beats/min), and three of the four ejection phase indexes showed improvement over control values during digoxin therapy.

Discussion

Intravenous versus oral administration of digoxin: The effect of digitalis preparations on the normal heart has been the subject of considerable controversy. Earlier studies using acute intravenous administration of digitalis demonstrated no consistent increase in cardiac output in either normal subjects or patients with mitral stenosis.[7,8] However, subsequent studies using more sensitive measures demonstrated increases in right and left ventricular performance after intravenous administration of digitalis.[9] In patients without congestive heart failure, the positive inotropic effect of acute digitalis administration was probably masked by increased peripheral vasoconstriction, which prevented an augmentation in cardiac output. By contrast, patients with congestive heart failure demonstrate increased cardiac output and reduced peripheral vascular resistance after administration of digitalis.[10] Therefore, the hemodynamic status of the patient is an important determinant of the net effect of digitalis on the heart and circulation.

In normal subjects there may also be a difference in the effects of intravenous and long-term oral administration of digitalis. Vatner et al.[11] demonstrated that digitalis given intravenously caused only minor positive inotropic effects in conscious animals with intact reflexes compared with the major increases seen in anesthetized animals. However, Mahler et al.[12] in our laboratory recently studied the effects of long-term digoxin administration in the conscious dog and demonstrated increases in several measures of myocardial performance in the resting state and during acute pressure loading. They postulated that decreased cardiac and circulatory reflexes during chronic digoxin administration may unmask the positive inotropic effects of the drug.

Our results demonstrate that oral maintenance digoxin therapy causes a modest but highly significant improvement in left ventricular performance in normal human subjects after acute pressure loading. This improvement was largely due to improved systolic shortening of the myocardium since there were no changes in end-diastolic dimension or ejection time. These results are in general agreement with previous data from our laboratory in normal conscious dogs.[12] The magnitude of the mean augmentation of the normalized rate of left ventricular dimension shortening during digoxin therapy as compared with the control rate during pressure loading was quite comparable: 26 percent in the previous study[12] and 16 percent in this study. Similar but less marked changes were observed during the basal state in both studies.

Heart rate as a source of variability: One possible source of variability in the response to digoxin in individual subjects was the inability to match consistently heart rates in control and digoxin periods. We have previously demonstrated the marked effect of changes in heart rate on various echocardiographic indexes of left ventricular performance.[3] In the previously instrumented conscious dog, heart rates were accurately matched with use of atrial pacing.[12] The effect of nonmatched heart rates was particularly evident in Subject 3, who showed increases in all four measures of left ventricular performance during digoxin therapy in the first study when his heart rate was 54 beats/min during the control period in the basal state and 55 beats/min during digoxin therapy. During his second study all four measures were depressed when his heart rate was 45 beats/min with digoxin compared with 53 beats/min in the control period. Furthermore, the three subjects whose heart rate was slower by 6 or more beats/min during digoxin therapy with acute pressure loading were the only inconsistent responders during this part of the study. Therefore, it is likely that variations in heart rate contributed to some of the inconsistent individual results in this study.

Other sources of variability: The complex effects of digoxin on the heart and peripheral circulation may also explain some of the variability it effects in some persons. In addition to heart rate, it was possible to control certain other variables more closely in the conscious dog. For example, before pressure loading the dogs were given volume infusions to insure adequate venous return and prevent wide fluctuations in left ventricular end-diastolic pressure. Systemic vascular resistance was not measured in our study, but alterations in this variable are known to affect left ventricular performance and increases in vascular resistance

have been demonstrated with intravenously administered digoxin.[10] If increased peripheral vascular resistance occurred during long-term oral digoxin therapy in some of our subjects, it may have negated any positive inotropic response to the drug. Similarly, changes in autonomic tone induced by digoxin or spontaneous variations in sympathetic nervous system activity for other reasons may have contributed to the inconsistent responses observed in some of our subjects.

Use of echocardiography: Our results are also in general agreement with the observation that 0.5 mg/day of orally administered digoxin produced a significant decrease in the ratio of left ventricular preejection period to ejection time in patients with compensated heart disease, but no change in ejection time alone.[13] This ratio is inversely related to ejection fraction determined angiographically.[14] However, by providing anatomic detail of a left ventricular minor diameter throughout the cardiac cycle, echocardiography can provide additional measures of left ventricular performance that are potentially more useful than systolic time intervals for studying the effects of various drugs on the heart.[15] The reproducibility and accuracy of these echocardiographic measures have been demonstrated by others,[16] and we have confirmed these findings in our own laboratory (unpublished data). Recently, Gomes et al.[17] demonstrated improvement in several echocardiographic measures of left ventricular performance and size in addition to a reduction in the preejection period/ejection time ratio in a few patients with congestive heart failure given digoxin orally. Delgado et al.[18] found in normal subjects ingesting alcohol that echocardiography detected a small but significant decrease in left ventricular performance despite an increase in heart rate; they also found an increased preejection period/ejection time ratio. Furthermore, preliminary work from our laboratory[19,20] has shown the utility of echocardiography for studying the effects of other cardioactive agents. Thus, although great care must be taken to ensure reproducible conditions and high quality recordings in each subject, we believe that echocardiography can provide reliable information on changes in left ventricular performance induced by cardioactive drugs such as digoxin.

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Electrophysiologic Effects of Atropine on Sinus Node and Atrium In Patients With Sinus Nodal Dysfunction

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Electrophysiologic studies were conducted in 21 patients with sinus nodal dysfunction before and after intravenous administration of 1 to 2 mg of atropine. The mean sinus cycle length (± standard error of the mean) was 1,171 ± 35 msec before and 806 ± 29 msec after administration of atropine ($P < 0.001$). Mean sinus nodal recovery time determined at a paced rate of 130/min and maximal recovery time were, respectively, 1,426 ± 75 and 1,690 ± 100 msec before and 1,169 ± 90 and 1,311 ± 111 msec after atropine ($P < 0.001$ and < 0.001). Mean calculated sinoatrial conduction time, measured in 16 patients, was 113 ± 8 msec before and 105 ± 9.7 msec after atropine (difference not significant). Mean atrial effective refractory period, measured at an equivalent driven cycle length, was 262 ± 11.1 msec before and 256 ± 10.3 msec after atropine (not significant). Mean atrial functional refractory period was 302 ± 12.5 msec before and 295 ± 11.3 msec after atropine (not significant).

The shortening of sinus cycle length and sinus recovery time with atropine was similar to that noted in patients without sinus nodal dysfunction. In contrast, atropine had insignificant effects on sinoatrial conduction and atrial refractoriness in this group whereas it shortens both in normal subjects. This finding may reflect altered perinodal and atrial electrophysiologic properties in patients with sinus node disease.

Earlier studies concerning the effects of atropine on the normal human sinus node and atrium were limited to direct observations of changes in sinus cycle length and indirect observation of atrial refractoriness based upon electrocardiographic behavior of atrial flutter and fibrillation before and after administration of atropine.[1–8] Recent catheter techniques allow more direct measurement of sinus nodal and atrial function. Techniques currently used include measurement of sinus nodal recovery time, indirect calculation of sinoatrial (S-A) conduction time and direct measurement of atrial refractoriness.[9–11] In patients without sinus node disease, atropine usually decreases both sinus nodal recovery time and sinoatrial conduction time and facilitates intra-atrial conduction.[12,13] In patients with sinus nodal dysfunction, atropine usually shortens sinus nodal recovery time, although paradoxic responses have been described.[12,14,15] Reported data concerning the effects of atropine on calculated S-A conduction time in patients with sinus nodal dysfunction are limited to a preliminary report with small number of patients,[16] and data concerning the atrial effects of atropine are not available.

In this study, we have used atrial stimulation techniques to evaluate systematically the electrophysiologic effects of atropine on the sinus node and atrium in patients with sinus nodal dysfunction. We have also contrasted these effects of atropine with those in patients without sinus node disease.

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Methods

The study group consisted of 21 patients undergoing electrophysiologic studies because of sinus nodal dysfunction. Criteria for inclusion in the study included the presence of either or both: (1) persistent resting sinus bradycardia (heart rate less than 60/min) or (2) documented episodes of S-A block or sinus arrest, or both, with or without symptoms. There were 19 men and 2 women whose ages ranged from 36 to 71 years (mean 59 ± 2 years). All patients had sinus rhythm and had taken no cardiac medication within 72 hours of the electrophysiologic studies. Informed written consent was obtained from all patients.

His bundle electrograms were recorded using a tripolar catheter passed through the femoral vein.[9] A quadripolar catheter was positioned at the high right atrium near the vicinity of the sinus node for atrial pacing (distal two poles) and for recording high right atrial electrograms (proximal two poles). Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-20 Electronics for Medicine) at paper speeds of 100 and 200 mm/sec. Simultaneous electrocardiographic leads I, II, III and V_1 were also recorded.

Atrial pacing was performed at increasing rates in increments of 10 beats/min. Sinus nodal recovery time was defined as the interval between the last paced P wave to the first spontaneous P wave after sudden cessation of pacing at rates ranging from 60 to 150 beats/min. For purposes of comparison, sinus nodal recovery time at a paced rate of 130/min was utilized.[9] Three sinus recovery times were determined at this rate and then averaged for each patient. Maximal sinus nodal recovery time was defined as the longest asystolic period after sudden cessation of pacing at any of the tested heart rates.

Atrial effective and functional refractory periods were measured with atrial extrastimulus techniques as previously described.[10] The following definitions were used in relation to atrial refractory periods: A_1, the atrial electrogram of spontaneous sinus or driven beats (S_1); A_2, the atrial electrogram in response to the extrastimulus (S_2); atrial effective refractory period, the longest S_1-S_2 interval at which S_2 did not result in atrial capture, atrial functional refractory period, the shortest attainable propagated A_1-A_2 interval. Refractory periods were measured during sinus rhythm in all patients, and in 20 patients at an atrial driven cycle length so that refractory periods could be measured at identical cycle lengths before and after administration of atropine.

Sinus nodal responses to atrial extrastimuli were categorized as previously described,[11] by noting the time of occurrence of the first spontaneous sinus beat (A_3) after A_2. Thus: (1) Nonreset due to sinus interference was defined when A_3 occurred at an A_2-A_3 interval of more than the spontaneous sinus cycle (A_1-A_1) and A_1-A_3 (coupling interval A_1-A_2 + return cycle A_2-A_3) equaled 2× (A_1-A_1). (2) Sinus reset was defined when A_2-A_3 was either equal to or more than A_1-A_1, and A_1-A_3 was less than twice A_1-A_1. (3) Sinus interpolation was defined when A_2-A_3 was less than A_1-A_1 and A_1-A_3 was either equal to A_1-A_1 (complete interpolation) or more than A_1-A_1 (incomplete interpolation). For purposes of analysis both complete and incomplete interpolation were grouped together. (4) Sinus echoes were defined when A_1-A_3 interval was less than A_1-A_1 and the P wave configuration of A_3 approximated that of the normal P wave with a high to low sequence of atrial activation. A_1-A_3 responses were plotted against A_1-A_2 coupling intervals as previously described.[11]

Each patient was categorized as to whether or not he had these zones. In each patient, a zone could be defined by its longest and shortest A_1-A_2 coupling interval and in terms of its absolute duration. When all patients with a given zone were considered, the zone could be described in terms of both mean longest and shortest A_1-A_2 coupling intervals and mean absolute duration. The magnitude of each zone was also compared in terms of percent of sinus cycle length both before and after administration of atropine.

Sinoatrial conduction time was calculated utilizing the atrial extrastimulus technique as described by Strauss et al.[17] For each patient, this was obtained by measuring the difference between the A_2-A_3 and A_1-A_1 intervals during the zone of reset and dividing by 2. A mean sinoatrial conduction time was calculated for each patient using all reset responses (normal mean ± standard deviation 92 ± 30 msec).[11]

Atropine was administered intravenously (a dose of 2 mg to patients under 60 years of age, and 1 mg to patients 60 and over) after control recordings were obtained. Measurements were initiated at 5 to 10 minutes after administration of atropine. Student's paired *t* test was used to analyze statistical significance of the data.

TABLE I

Summary of Electrophysiologic Findings (mean ± standard error of the mean) After Atropine

	no.	Control	After Atropine	*P* Value
Sinus cycle length (msec)	21	1171 ± 35	806 ± 29	<0.001
Sinus recovery time (msec)	21	1426 ± 75	1169 ± 90	<0.001
Maximal sinus recovery time (msec)	21	1690 ± 100	1311 ± 111	<0.001
Calculated SACT (msec)	16	113 ± 8	105 ± 9.7	NS
Atrial ERP (NSR) (msec)	21	325 ± 13.8	293 ± 14.7	<0.02
Atrial FRP (NSR) (msec)	21	381 ± 13.2	349 ± 15.7	<0.02
Atrial ERP (at equivalent CL) (msec)	20	262 ± 11.1	256 ± 10.3	NS
Atrial FRP (at equivalent CL) (msec)	20	302 ± 12.5	295 ± 11.3	NS

CL = cycle length; ERP = effective refractory period; FRP = functional refractory period; no. = number of patients; NS = not significant; NSR = normal sinus rhythm; *P* = probability; SACT = sinoatrial conduction time.

Results

Effect on Sinus Node (Table I)*

Sinus cycle length and recovery time: Control sinus cycle lengths ranged from 840 to 1,493 msec, with a mean (± standard error of the mean) of 1,171 ± 35 msec. After atropine, sinus cycle lengths ranged from 650 to 1,060 msec, with a mean of 806 ± 29 msec (P <0.001). Sinus cycle length decreased in all patients. Sinus nodal recovery time (at a paced rate of 130/min) ranged from 910 to 2,500 msec (mean 1,426 ± 75 msec) during the control state. After administration of atropine, recovery times ranged from 760 to 2,300 msec (mean 1,169 ± 90 msec) (P <0.001). Sinus recovery time decreased in all but one patient (Case 2), whose recovery time paradoxically increased from 1,655 to 1,900 msec after the drug. Maximal sinus nodal recovery time

* The detailed data for individual patients are available on request from the author.

ranged from 1,200 to 3,020 msec before atropine (mean 1,690 ± 100 msec). Maximum sinus node recovery time decreased significantly after atropine, ranging from 760 to 3,100 msec (mean 1,311 ± 111 msec) (P <0.001). Maximal sinus recovery time decreased in all but one patient (Case 7), whose maximal recovery time increased from 2,500 to 3,100 msec after administration of atropine.

Sinus responses to extrastimuli: A zone of nonreset due to interference was defined in all 21 patients during the control state and in 20 patients after administration of atropine. In one patient, the postextrasystolic beat was of junctional rather than sinus origin after atropine (Case 19). The mean zone of interference in the 20 patients was between 1,158 msec (outer limit) and 894 msec (inner limit) with an absolute duration of 264 msec at a mean sinus cycle length of 1,158 msec before atropine (Fig. 1). After administration of atropine, the zone of interference in these patients ranged from 792 msec (outer limit) to 540 msec (inner limit) with an absolute duration of 252 msec at a mean sinus cycle of 792 msec (difference not significant). This zone accounted for the last 23 percent of the sinus cycle length before and 32 percent of the sinus cycle length after administration of atropine (P <0.01).

A zone of sinus reset was present in all patients during the control state and in only 16 patients after administration of atropine. The five patients whose sinus reset responses could not be delineated after administration of the drug included one whose return beats were junctional, and four others (Cases 2, 7, 8 and 14), whose zone of interference accounted for 100 percent of the scanned sinus length (zone I response) (Fig. 2). In these latter four patients, the inner limit of the zone of interference was the atrial functional refractory period, which was lengthened in all after administration of atropine. These four patients included the two with paradoxical lengthening of sinus nodal recovery time. The mean zone of reset in the 16 patients with reset responses before and after atropine was between 904 msec (outer limit) and 404 msec (inner limit) before atropine, with an absolute duration of 500 msec at a mean sinus cycle length of 1,145 msec (Fig. 1). The mean zone of reset after atropine was between 551 msec (outer limit) and 328 msec (inner limit) with an absolute duration of 223 msec at a mean sinus cycle length of 769 msec (P <0.001). The zone of reset accounted for 43 percent of sinus cycle length before and 29 percent after administration of atropine (P <0.001).

Sinus interpolation (total or partial) was defined in four patients before administration of atropine. In two of these, interpolation responses were abolished with atropine, and in two the zone was unchanged. One patient had interpolation responses only after atropine.

Sinus echoes were present in two patients during the control state. Atropine abolished the sinus echo responses in one of these. In the other patient, there was no change in the magnitude of the sinus echo zone after administration of atropine. No patient had a new echo zone after atropine.

Atrial Effects

Calculated S-A conduction time: The effect of atropine on calculated S-A conduction time was evaluated

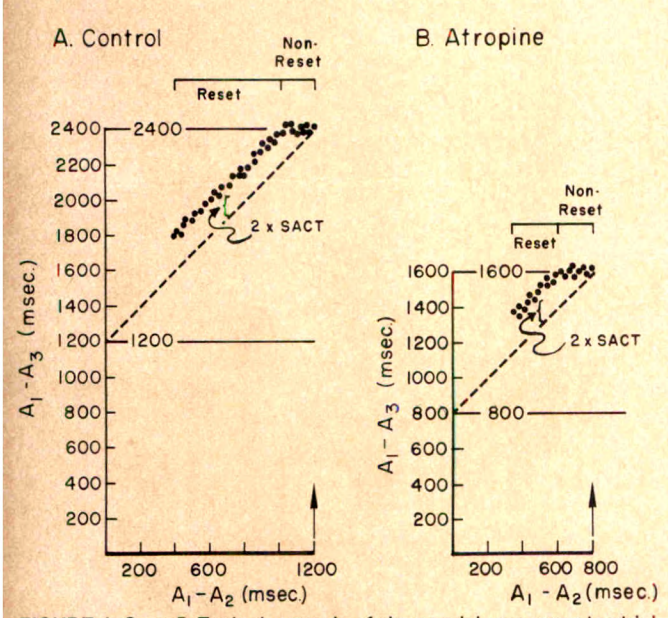


FIGURE 1. Case 5. Typical example of sinus nodal responses to atrial extrastimuli during sinus rhythm before and after administration of atropine. A_1-A_3 responses are plotted on the ordinate as a function of the test cycle (A_1-A_2) on the abscissa. **Panel A** (before atropine), the sinus cycle is 1,200 msec. The zone of nonreset due to interference (zone 1) ranges from 1,200 to 1,030 msec. The zone of reset is between 1,020 and 390 msec; the sinoatrial conduction time (SACT) is 80 msec. **Panel B** (after atropine), the sinus cycle is 800 msec. The zone of nonreset ranges from 800 to 600 msec, and the zone of reset is between 590 and 340 msec. The sinoatrial conduction time is 100 msec.

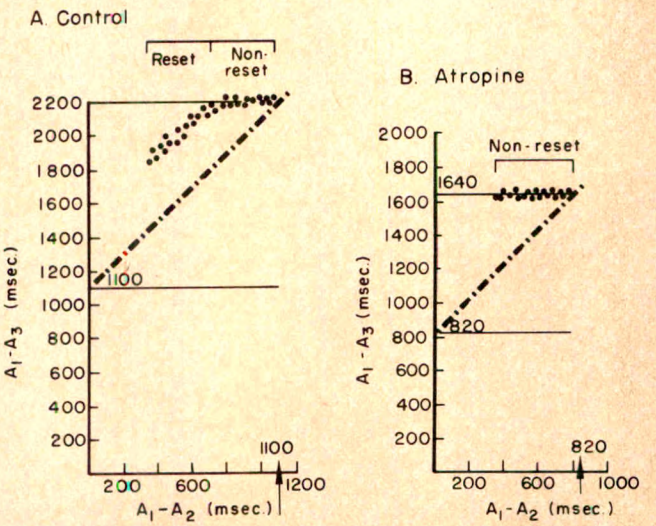


FIGURE 2. Case 7. Demonstration of zone 1 response after atropine. **Panel A** (before atropine), the sinus cycle is 1,100 msec. The zone of nonreset ranges from 1,100 to 720 msec, and the zone of reset is between 710 and 350 msec (the atrial functional refractory period). The sinoatrial conduction time is 210 msec. **Panel B** (after atropine), the sinus cycle is 820 msec, and the zone of interference ranges from 820 to 380 msec; the latter defines the atrial functional refractory period. Note the absence of zone of reset.

in all patients during the control state and in 16 patients (with reset responses) after administration of atropine. The S-A conduction time in these 16 patients during the control state ranged from 70 to 170 msec (mean 113 ± 8 msec). After administration of atropine, it ranged from 60 to 175 msec (mean 105 ± 9.7 msec) (not significant) (Fig. 1 and 3). Calculated S-A conduction time decreased in nine and increased in seven patients after atropine.

Atrial refractory periods: Atrial effective and functional refractory periods were measured in all patients during sinus rhythm. During sinus rhythm, atrial effective refractory periods ranged from 210 to 480 msec (mean 325 ± 13.8 msec). After atropine (during sinus rhythm), atrial effective refractory periods ranged from 200 to 480 msec (mean 293 ± 14.7 msec) ($P < 0.02$). Atrial functional refractory periods before atropine ranged from 280 to 520 msec (mean 381 ± 13.2 msec) and after atropine, from 260 to 500 msec (mean 349 ± 15.7 msec) ($P < 0.02$).

Atrial effective refractory periods at identical driven cycle length (mean cycle length 535 msec) in 20 patients ranged from 170 to 350 msec (mean 262 ± 11.1 msec) before atropine, and from 170 to 340 msec (mean 256 ± 10.3 msec) after atropine (not significant) (Fig. 4, B and D). Atrial functional refractory period in these patients ranged from 200 to 410 msec (mean 302 ± 12.5 msec) before atropine and from 200 to 390 msec (mean 295 ± 11.3 msec) after atropine (not significant) (Fig. 4, A and C). No change in P wave duration or configuration was noted after atropine administration.

Discussion

Atropine has been used in patients with sinus node disease both therapeutically and diagnostically.[6,8,18–21] Therapeutically, atropine has been shown to be capable of increasing sinus rates in some patients with sinus node disease.[8,18–21] Diagnostically, it has been suggested that a blunted acceleration in sinus rate after administration of atropine indicates sinus nodal dysfunction.[18–22] Bradycardia in patients with sinus node disease may be the result of depressed sinus automaticity or S-A block, or both. Vagotonia may play a role in either or both of these circumstances. The positive chronotropic action of atropine in these patients presumably reflects vagolysis.

Sinus rate: Although considerable data are available concerning the effect of atropine on sinus nodal function

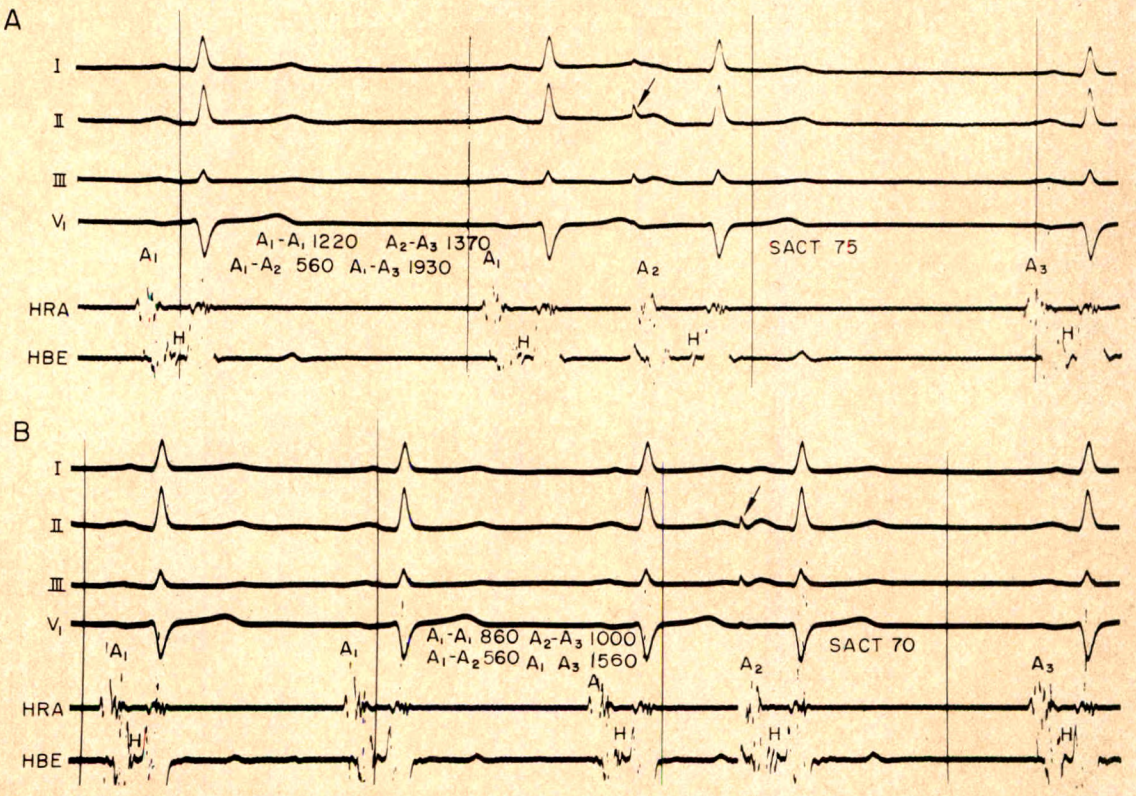


FIGURE 3. Case 12. Measurements of sinoatrial conduction time before and after administration of atropine in a typical case. Shown are electrocardiographic leads I, II, III and V_1, a bipolar intracardiac high right atrial electrogram (HRA), and a His bundle electrogram (HBE). A_1 is the atrial electrogram of spontaneous sinus beat, A_2 is the response to the extrastimulus and A_3 is the return cycle. His bundle potentials are labeled H. Paper speed is 100 mm/sec and time lines are at 1 second intervals. The sinus cycle length (A_1-A_1), atrial coupling interval (A_1-A_2), return cycle length (A_2-A_3), combined coupling and return cycle length (A_1-A_3) and calculated sinoatrial conduction time (SACT) are listed on each panel. **Panel A** is the control recording; **panel B** was obtained after administration of atropine. **Panel A,** sinus rhythm with A_1-A_1 of 1,220 msec. At a coupling interval of 560 msec, A_2-A_3 is 1,370 msec, whereas A_1-A_3 of 1,930 msec is less than twice A_1-A_1. The sinus node is reset by A_2. The sinoatrial conduction time (half the difference between A_2-A_3 and A_1-A_1) is 75 msec before administration of atropine. **Panel B,** sinus rhythm after administration of atropine with A_1-A_1 of 860 msec. At a similar coupling interval of 560 msec, A_2-A_3 is 1,000 msec with reset of the sinus node. The calculated sinoatrial conduction time is 70 msec.

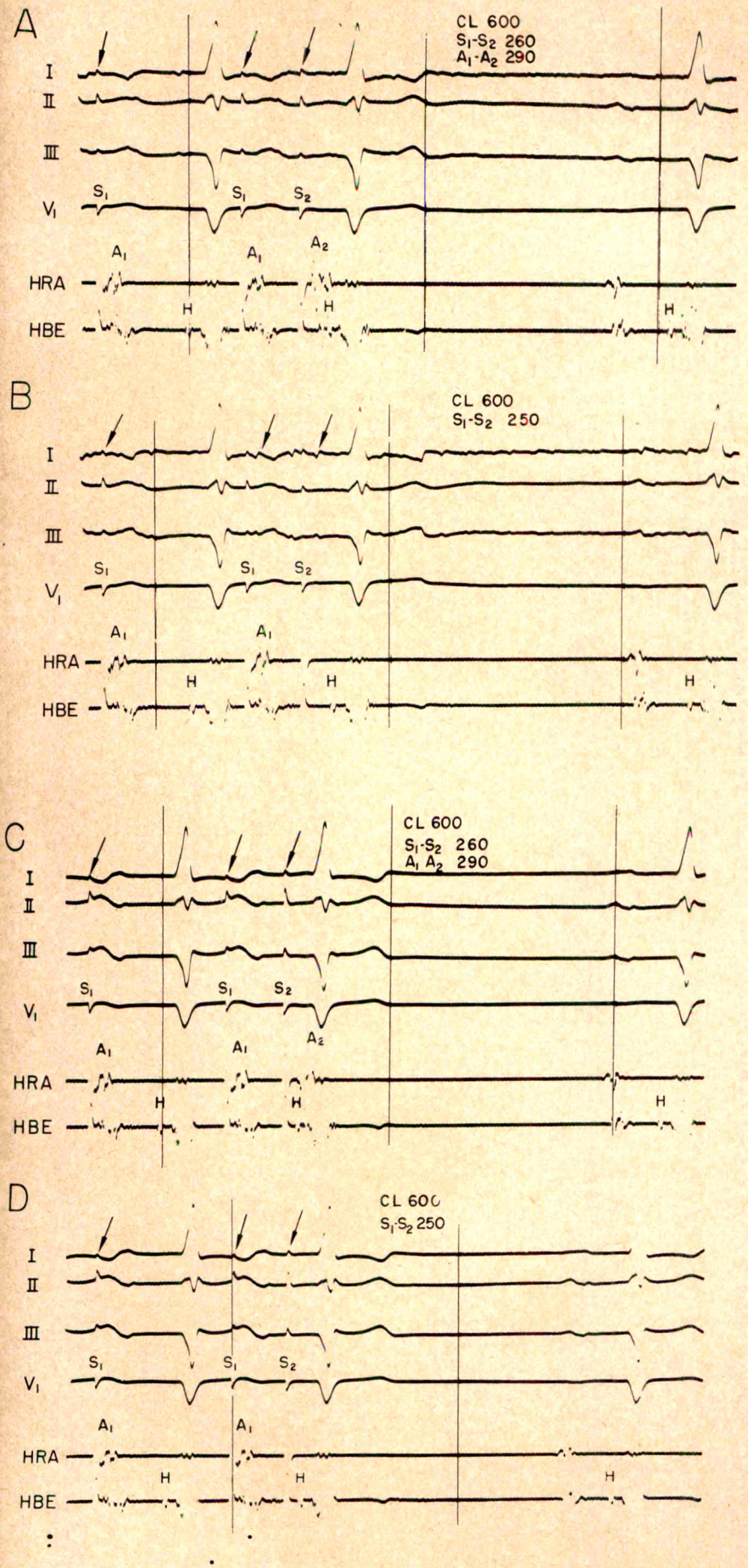


FIGURE 4. Case 3. Measurements of atrial refractory periods at equivalent cycle lengths before and after administration of atropine in a typical case. The cycle length (CL) of the basic drive (S_1) is 600 msec, and the extrastimulus and atrial coupling intervals (S_1-S_2 and A_1-A_2) are listed at the top of each panel. **Panels A and B** are control recordings; **panels C and D** were obtained after administration of atropine. **Panel A,** at a coupling interval of 260 msec, S_2 is conducted to the atrium. A_1-A_2 is 290 msec and is the shortest attainable A_1-A_2 interval, defining the functional refractory period of the atrium before administration of atropine. **Panel B,** S_2 fails to capture the atrium at a coupling interval of 250 msec. This defines the effective refractory period of the atrium before atropine. **Panel C,** at a coupling interval of 260 msec, S_2 is conducted to the atrium with an A_1-A_2 of 290 msec, which is the shortest attainable A_1-A_2 interval, defining the functional refractory period of the atrium after administration of atropine. **Panel D,** S_2 fails to capture the atrium at a coupling interval of 250 msec, defining the effective refractory period of the atrium after atropine.

in patients without sinus node disease, information on patients with sinus nodal dysfunction is limited.[6,7,12–16] It has been demonstrated that atropine increases sinus rates by 20 to 40 percent in patients with normal sinus nodal function.[2–8,23–26] In 11 patients with symptomatic sinus node disease, Rosen et al.[18] demonstrated increase in heart rates of 25 to 125 percent after 1 mg of atropine, but in none of these patients did the rate increase to more than 90 beats/min. Mandel et al.[20] reported an average increase in heart rate of 12 beats/min after administration of 0.025 mg/kg of atropine in 31 patients with the sick sinus syndrome. Our study is in agreement with these previously reported studies. Although we demonstrated an increase of 45 percent in sinus rate in our patients with sinus bradycardia, in only two was the rate increased to more than 90 beats/min. It has previously been shown in both experimental animals and man that atropine could cause paradoxical slowing of heart rate.[26–29] We found no such paradoxical responses, sinus rates increasing in all of our patients.

Sinus nodal recovery time: It has been previously demonstrated that atropine shortens sinus nodal recovery time in patients with normal sinus nodal function. Mandel et al.[12] reported shortening of recovery time in six patients with normal sinus nodal function. In another study of 17 patients without sinus node disease, Dhingra et al.[13] demonstrated an average 25 percent decrease in sinus recovery time after administration of atropine. The effects of atropine on sinus recovery time in patients with sinus nodal dysfunction are variable. Recovery times may shorten, remain unchanged or may paradoxically lengthen. Mandel et al.[12] demonstrated shortening of recovery time in two patients with the sick sinus syndrome. Narula et al.[30] reported the effects of atropine on corrected sinus nodal recovery time in 10 patients with sinus bradycardia. In three of these, the corrected recovery time after atropine was shortened, in two it was unchanged and in one it was prolonged. In the remaining four patients, junctional escape beats terminated the postpacing pause after atropine. Both Bashour et al.[14] and Reiffel et al.[15] reported one case with paradoxic prolongation of sinus recovery time after atropine. This paradoxic lengthening was thought to reflect decreased sinus entrance block with atropine, allowing more driven atrial impulses to penetrate the sinus node, resulting in increased recovery time. In our study, both sinus recovery time and maximal sinus recovery time decreased with atropine in most patients. This abbreviation of sinus recovery time is presumably related to enhancement of sinus automaticity.

S-A conduction time: Relatively little information is available concerning the effect of atropine on calculated S-A conduction time in patients with or without sinus node disease. In a study of 17 patients without sinus node disease, we recently demonstrated an average 43 percent decrease in calculated S-A conduction time after administration of atropine.[13] The decrease in conduction time was present in all the patients. Reiffel et al.[16] reported similar effects of atropine in a study of 15 patients with sinus bradycardia. In another patient with sick sinus syndrome described by the same workers,[15] 1 mg of atropine decreased calculated sinoatrial conduction time from 83 to 75 msec. The results of our study are in contrast with these previous findings. Calculated sinoatrial conduction time was unchanged with atropine in our patients with sinus node disease. However, since it has been suggested in man that calculated sinoatrial conduction time prolongs with spontaneous decrease in cycle length, the unchanged sinoatrial conduction despite decrease in cycle length suggests some facilitation of sinoatrial conduction with atropine.[31]

Zones of sinus nodal responses: Information regarding effects of atropine on individual zones of sinus nodal responses is limited to patients without sinus nodal dysfunction.[13] The zone of sinus nonreset due to interference (or zone 1) represents a period late in atrial diastole, in which the incoming impulses (A_2) collide (presumably in the perinodal fibers) with the outgoing sinus impulses and are thus unable to reset the sinus node.[32–34] The duration of this zone is approximately twice calculated sinoatrial conduction time.[11] It has been shown[13] that atropine causes shortening of this zone along with decreasing sinoatrial conduction time in patients without sinus node disease. In our present study of patients with sinus nodal dysfunction, atropine caused no absolute change in the zone of interference (since atropine did not significantly affect sinoatrial conduction time), but did cause a percentage increase due to shortening of sinus cycle length.

The zone of reset represents a period in atrial diastole in which incoming premature impulses (A_2) are able to penetrate and reset the sinus node. The decrease in this zone (both absolute and percent decrease) reflected the shortening of cycle length, the lack of change in the zone of interference (the outer limit of the zone of reset), and the small changes in atrial functional refractory period (the inner limit of this zone in most of the patients). These observations suggest that sinus sensing (or resetting) is decreased with atropine in patients with sinus bradycardia. This is in contrast to the results of Smith et al.,[35] who demonstrated increased sinus nodal sensing with atropine in patients with normal sinus nodal function.

The four patients who manifested zone 1 responses after atropine are of interest. This phenomenon primarily reflected shortening of cycle length, coupled with an unchanged absolute zone of nonreset, and the small change or increase in atrial functional refractory period. This resulted in total elimination of reset responses. If atrial functional refractory periods had shortened with atropine in these patients, presumably reset responses would have been identified.

Zones of interpolation (unidirectional sinus block) and echoes probably reflect increased refractoriness of perinodal fibers.[32–34] In patients without sinus node disease, these responses are eliminated by atropine, presumably reflecting facilitation of perinodal conduction (decrease in sinoatrial conduction time).[13] Interpolation and echo responses were unaffected by atropine in patients with sinus bradycardia, probably

because of its minimal action on perinodal conduction.

Atrial refractory periods: Data concerning the effect of atropine on the electrophysiologic properties of the human atrium are limited. Akhtar et al.[36] determined, in nine patients without sinus node disease, the atrial refractory period at a driven cycle length of 600 msec and reported variable effects of atropine. In their study, the atrial effective refractory period decreased in four, increased in three and were unchanged in two patients. Bissett et al.,[37] studying six patients with normal sinus nodal function at equivalent driven cycle lengths, found no significant effect of atropine on atrial effective refractory period. We have recently shown in a study of 17 patients without sinus node disease that both atrial effective and functional refractory periods measured at equivalent driven cycle lengths significantly shortened with atropine,[13] an action opposite to that reported in experimental animals.[38–40] Our present data in patients with sinus nodal dysfunction are in contrast with those from our patients with normal sinus nodal function. Atropine did not produce any significant change in atrial effective and functional refractory periods at equivalent driven cycle lengths in patients with sinus bradycardia. The significant decrease in atrial refractoriness observed in our patients during sinus rhythm probably reflected shortening of cycle length after administration of atropine.[11]

Our study demonstrates that some of the effects of atropine on the atrium and sinus node in patients with and without sinus nodal dysfunction are dissimilar. In our previous study, we demonstrated that atropine significantly shortened sinoatrial conduction time and atrial refractory periods in patients with normal sinus nodal function.[13] Lack of these effects in patients with sinus nodal dysfunction suggests the presence of associated atrial and perinodal fiber disease with altered electrophysiologic properties. This would partially explain the previously described therapeutic ineffectiveness of atropine in some patients with the sick sinus syndrome.[41]

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Vein Graft Patency and Intimal Proliferation After Aortocoronary Bypass: Early and Long-Term Angiopathologic Correlations

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To determine the clinical significance of intimal proliferation as a cause of aortocoronary bypass vein graft obstruction, 492 vein grafts from 281 patients were studied 0 to 75 months postoperatively. All grafts had been inserted between 1968 and 1975 by one surgeon using one technique. The graft patency rate was 92 percent (55 of 60) in the first month; 91 percent (49 of 54) at 1 to 3 months; 84 percent (37 of 44) at 4 to 6 months; 77 percent (33 of 43) at 7 to 12 months; 81 percent (113 of 140) at 13 to 24 months; 82 percent (59 of 72) at 25 to 36 months; and 84 percent (66 of 79) at 37 to 75 months. Vein graft samples were obtained from 41 patients: In 27 patients with 51 grafts (early group), they were obtained 0 to 30 days (mean 14 days) postoperatively; in 14 patients with 27 grafts (late group) they were obtained 7 to 75 months (mean 34 months) postoperatively. Intimal proliferation was graded 1 to 4 corresponding to an intima/media thickness ratio of 1, 2, 3 or 4, respectively. In the early group, all 51 vein grafts showed grade 1 to 2 intimal proliferation; 5 of these grafts were occluded, all as a result of recent thrombosis. In the late group, 17 of the 27 grafts were studied histologically. All patent vein grafts showed grade 2 to 3 intimal proliferation. Four vein grafts were occluded but only one as a result of grade 4 intimal proliferation. In 14 patients in the late group, angiograms performed shortly before vein graft samples were obtained revealed 14 patent and 4 occluded vein grafts. Ten of the 14 patent vein grafts showed grade 2 to 3 intimal proliferation but were of uniformly good caliber angiographically (graft/artery ratio more than 1.5).

Thus, most graft occlusions occur early and are usually due to thrombosis. Late graft occlusion is uncommon and is rarely due to intimal proliferation. The angiographic appearance of vein grafts up to 75 months postoperatively suggests that intimal proliferation is not always progressive. Moderate to marked intimal proliferation is the usual finding in long-term grafts, but is compatible with good graft patency.

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Intimal proliferation has long been accepted as an ominous pathologic change in autogenous veins used as arterial bypass grafts. It was reported first in saphenous veins employed as femoropopliteal bypass grafts[1–3]; more recently, identical changes have also been noted in aortocoronary saphenous vein bypass grafts.[4–8]

Because intimal proliferation has been observed to have the potential for producing marked reduction in graft caliber even to the point of complete occlusion, it has been suggested that late graft occlusion in aortocoronary bypass from progressive intimal proliferation may be inevitable.[9] The aim of this study was to examine the influence of intimal proliferation on vein graft patency by early and long-term angiographic and histologic follow-up studies in a large group of patients.

Material and Methods

Between 1968 and 1975, aortocoronary saphenous vein bypass procedures were performed in 1,837 patients by one surgeon utilizing the same technique. The indication for operation was angina pectoris in all cases. There were 1,619 men and 218 women. The mean age at operation was 52.4 years (range 23 to 81 years). The surgical technique used has been described previously.[10] The veins were removed from the thigh by sharp dissection through multiple incisions with minimal handling of the vein. A solution of 0.1 mg heparin/ml normal saline solution at room temperature was used during preparation of the veins. Care was taken to avoid overdistension or crushing injury to the veins. Proximal and distal anastomoses usually were performed with continuous 6-0 Prolene® suture material, occasionally with continuous 7-0 nylon suture material. Postoperatively neither anticoagulant agents nor platelet aggregation inhibitors were used.

Graft patency was determined in 281 patients with 492 saphenous vein grafts a mean of 19 months after operation (range 0 to 75 months). Cineangiography was used to assess graft patency in 218 patients, including 23 patients with 36 grafts who had more than one study. In 186 of these patients the indication for restudy was recurrent chest pain; the remaining 32 patients were asymptomatic. Graft patency was assessed with percutaneous transfemoral aortic root angiography in 28 patients and determined at autopsy in 35.

Specimens of 68 vein grafts from 41 of the 281 patients were studied 0 to 75 months postoperatively; they were obtained at reoperation in 11 patients (11 specimens) and at autopsy in the remaining 30 (57 specimens). The patients were classified into two groups: early (27 patients with 51 specimens obtained a mean of 14 days [range 0 to 30 days] postoperatively) and late (14 patients with 17 specimens obtained a mean of 34 months [range 7 to 75 months] postoperatively). In 10 patients in the late group the cineangiograms obtained shortly before operation were available for angiopathologic correlation with the specimens obtained.

All vein graft specimens were fixed in buffered 10 percent formalin and cut into multiple 2 to 3 mm tissue blocks. Paraffin-embedded sections, cut at 5 to 7 μ were stained with hematoxylin-eosin, Movat's pentachrome, and phosphotungstic acid hematoxylin for routine light microscopy. The degree of intimal proliferation was graded 1, 2, 3 or 4 according to the intima/media thickness ratio (Fig. 1).

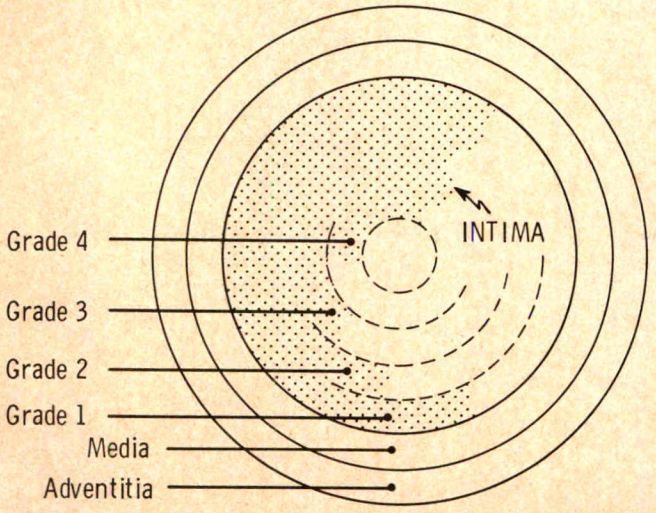


FIGURE 1. Method used to grade the severity of intimal proliferation according to intima/media thickness ratio.

Results

Patency rate: The overall graft patency rate was 84 percent (412 of 492 grafts) for the 19 month mean follow-up period (range 0 to 75 months); its relation to time is shown in Figure 2. The slightly lower patency rate at 7 to 12 months is attributable to the large incidence of symptomatic patients restudied at that time interval. The overall graft patency rate was 86 percent (67 of 78) in the 41 patients with histologic studies; the early patency rate was 90 percent (46 of 51) and late patency rate 78 percent (21 of 27).

Histologic evaluation of vein grafts (Table I): In the early group of 27 patients, all 51 vein grafts were examined histologically. All had intimal proliferation of grade 1 (23 grafts) or grade 2 (28 grafts). Five of these grafts were occluded, all as a result of recent thrombosis.

In the late group of 14 patients, 17 vein grafts were examined histologically (Table II). All grafts showed

TABLE I

Histologic Findings (Grade of Intimal Proliferation) in Grafts Studied Early and Late Postoperatively

Grade of Intimal Proliferation	Grafts (no.)	
	Early Group	Late Group
1	23	0
2	28	3
3	0	10
4	0	1
Total	51	14*

*Three grafts in the late group were occluded by well organized thrombus and could not be graded.

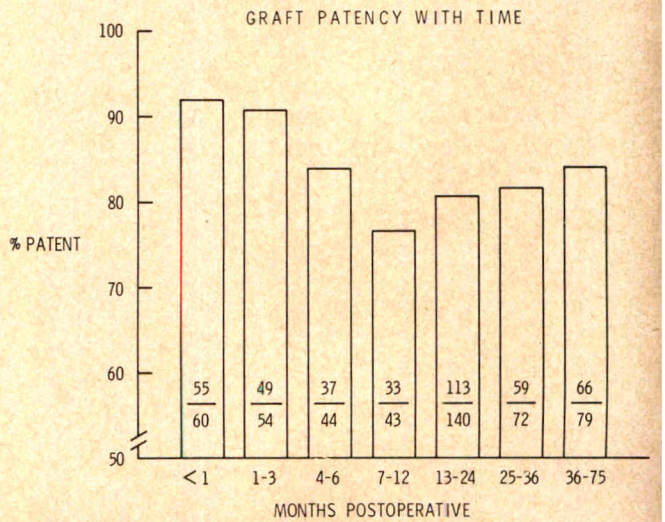


FIGURE 2. Relation of graft patency to time. Numbers in each bar represent the number of patent grafts/number of grafts studied. Note that the maximal decrease in patency occurs in the first 3 months postoperatively.

significant intimal proliferation (grade 2 or greater). Four grafts were occluded, only one as a result of grade 4 intimal proliferation with superimposed recent thrombosis, the other three grafts were occluded by old organized thrombosis.

Angiographic and histologic correlation: In the 10 patients in the late group (17 grafts) studied angiographically, 14 patent grafts were visualized. Ten of these 14 patent grafts were studied histologically, and despite grade 2 or 3 intimal proliferation, all 14 grafts showed very satisfactory patency on angiography. The typical angiographic appearance was smooth uniform reduction of caliber of mild degree and graft shortening (Fig. 3). Figures 4 to 7 show examples of correlative histologic and angiographic graft appearance 23, 30, 64 and 75 months, respectively, after operation.

TABLE II

Data in 14 Cases Studied Late (7 to 75 months) Postoperatively

Case no.	Site of Graft Studied	Months After Implantation	Specimen	Source	Patency	Histologic Changes*
1	RCA	7	Biopsy	Operation	Patent	3
2	RCA	17	Biopsy	Operation	Patent	3
3	RCA	23	Whole	Autopsy	Patent	2
	LAD	23	Whole	Autopsy	Occluded	Organized thrombus
4	RCA	32	Biopsy	Operation	Patent	3
5	RCA	8	Whole	Autopsy	Patent	3
	LAD	8	Whole	Autopsy	Patent	3
6	LAD	13	Biopsy	Operation	Patent	3
7	RCA	13	Biopsy	Operation	Patent	2
8	RCA	16	Whole	Autopsy	Patent	3
	LAD	16	Whole	Autopsy	Occluded	Organized thrombus
9	LAD	33	Biopsy	Operation	Patent	3
10	RCA	30	Biopsy	Operation	Patent	3
11	LAD	75	Biopsy	Operation	Patent	2
12	LAD	51	Whole	Operation	Occluded	4: recent thrombus
13	RCA	44	Biopsy	Operation	Occluded	Organized thrombus
14	LAD	64	Biopsy	Operation	Patent	3

*The numerals indicate grade of vein graft intimal proliferation as defined in the text and shown in Figure 1.
LAD = left anterior descending coronary artery; RCA = right coronary artery.

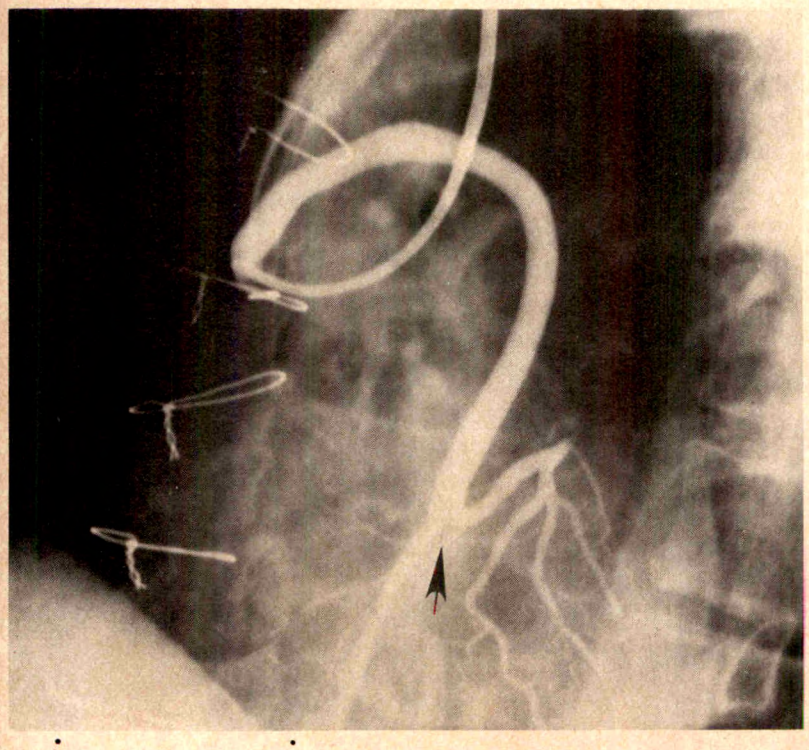


FIGURE 3. Twelve-month postoperative angiogram of vein graft to the left anterior descending coronary artery showing diffuse mild narrowing. Tenting up of the artery by the graft **(arrow)** indicates mild graft shortening secondary to intimal proliferation.

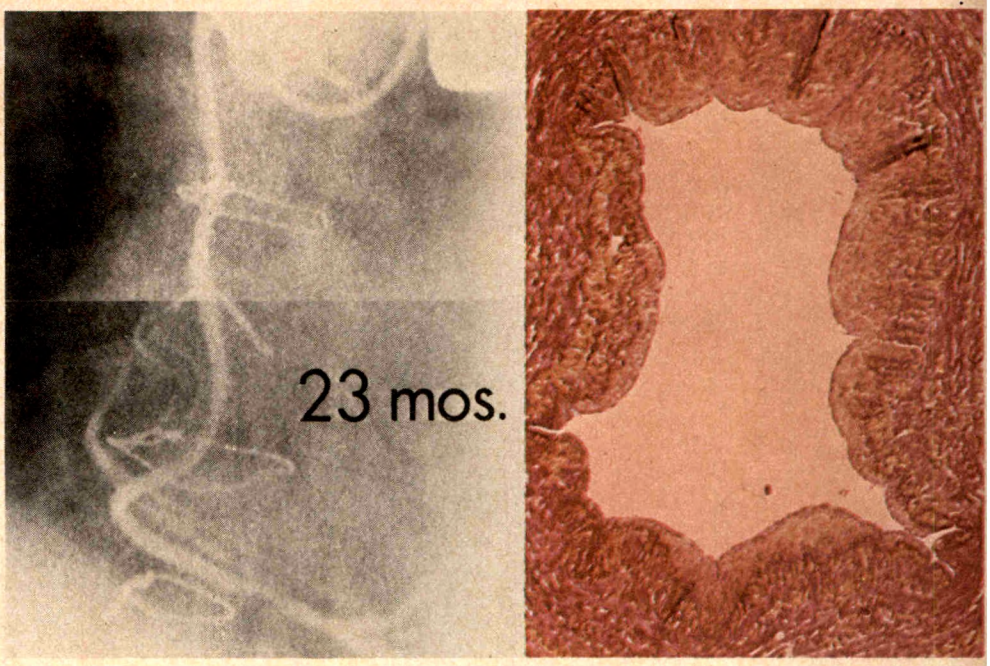


FIGURE 4. Case 3. Angiogram **(left)** and histologic section **(right)** of vein graft to the right coronary artery 23 months postoperatively.

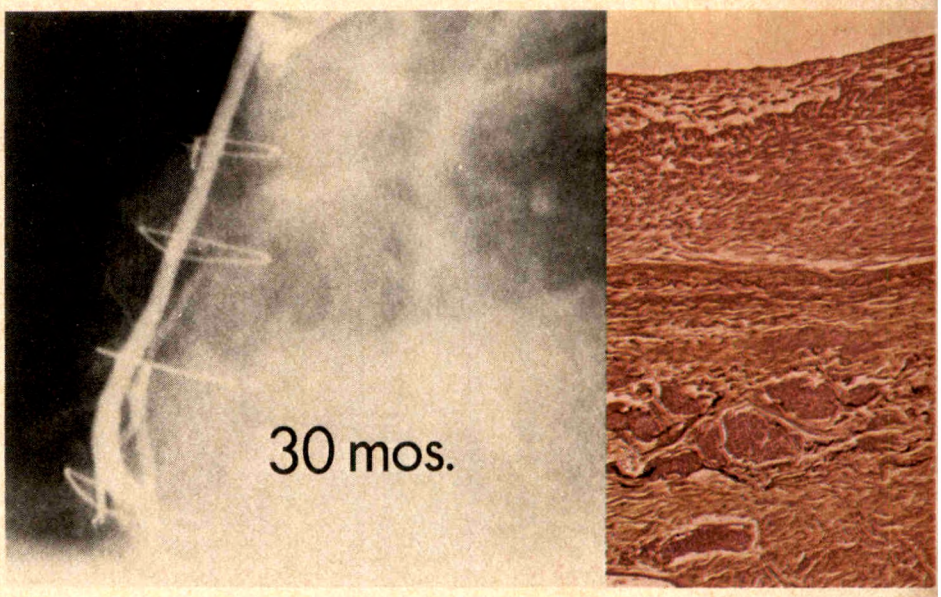


FIGURE 5. Case 10. Angiogram **(left)** and histologic section **(right)** of vein graft to the right coronary artery 30 months postoperatively.



FIGURE 6. Case 14. Angiogram **(left)** and histologic section **(right)** of vein graft to the left anterior descending coronary artery 64 months postoperatively.

From the angiopathologic correlation made in these 10 grafts from the patients in the late group, it was possible to estimate the extent of intimal proliferation in the overall group of patent grafts, visualized angiographically. In all but three of these grafts the lumen was smooth and uniform, graft diameter was greater than 1.5 times that of the recipient artery, and there were no significant segmental stenoses.

One of the angiographically abnormal vein grafts, from a patient with type IV familial hyperlipidemia, had an irregular reduction in graft lumen resembling that seen in the vein graft studies of a separate group of patients with hyperlipidemia (J. T. Lie et al., in preparation). The other two abnormal grafts were from a single patient; they had been created from very small saphenous veins and showed subtotal obstruction from diffuse narrowing.

Discussion

Although saphenous vein autografts have been used in peripheral vascular surgery for more than 70 years[11] and in coronary arterial surgery for more than 12 years,[12] considerable concern has been expressed in regard to their long-term behavior. Previous anatomic studies of selected material without the benefit of con-

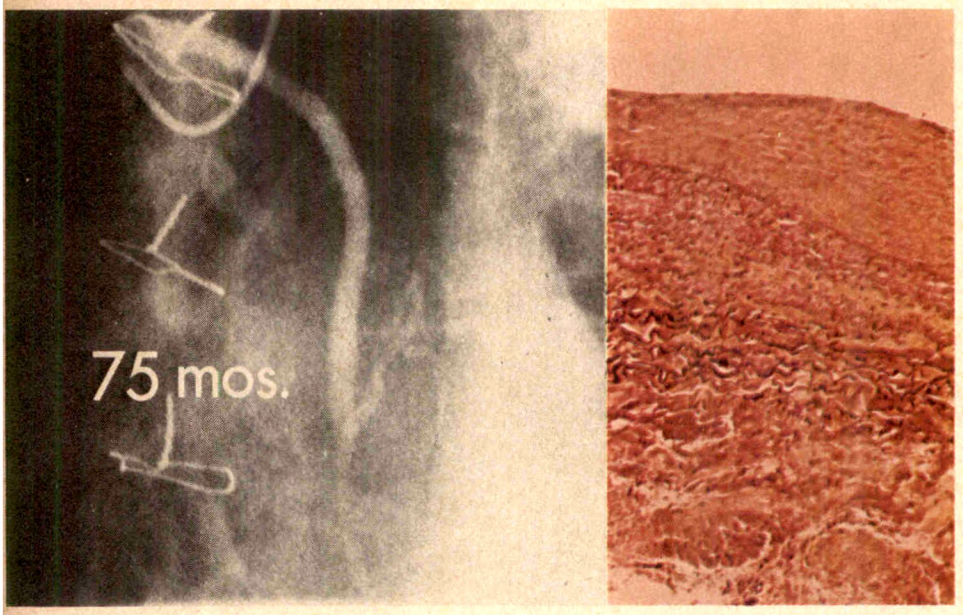


FIGURE 7. Case 11. Angiogram **(left)** and histologic section **(right)** of vein graft to left anterior descending coronary artery 75 months postoperatively.

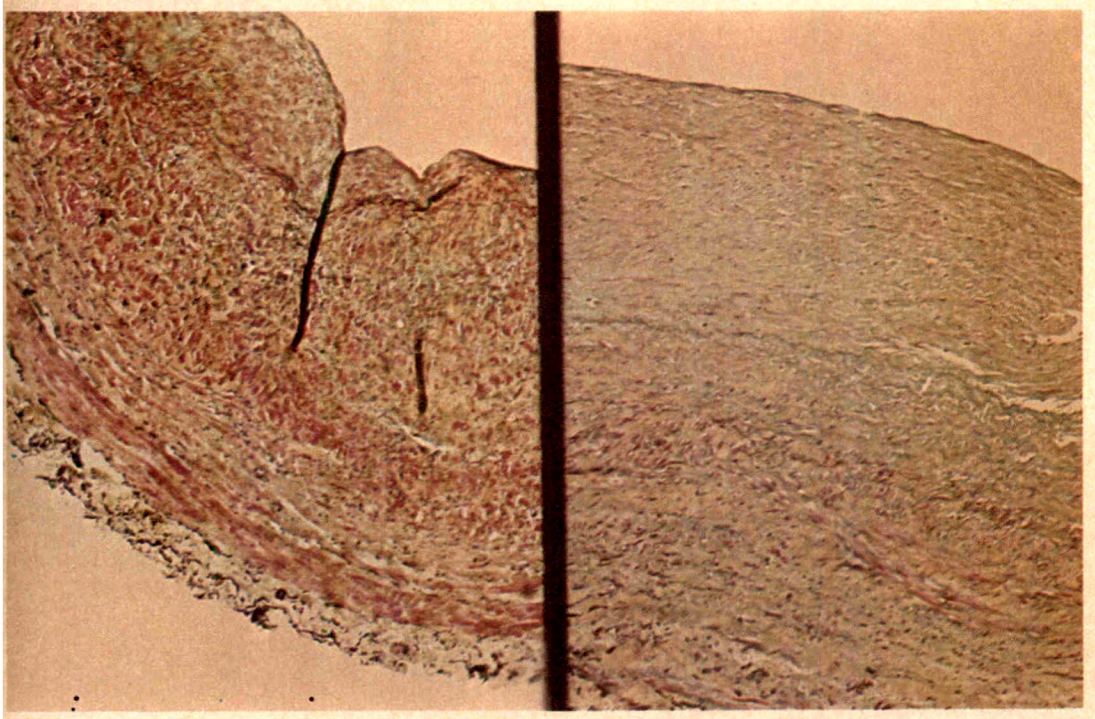


FIGURE 8. Comparison of the changes of intimal proliferation in a saphenous vein in its anatomic position **(left)** and from a 64 month old vein bypass graft **(right).** Both specimens were obtained from the same patient at the time of reoperation; both show grade 3 intimal proliferation.

current angiographic correlation may have been responsible for the view that there is frequent and inevitable progression of intimal proliferation to complete graft occlusion.[6,7,9]

The materials in our study, derived from a large homogenous group of patients and vein grafts, were obtained from a representative subgroup for angiopathologic correlation. Thus, it has been possible to obtain a more balanced view of the clinical significance of intimal proliferation as the cause of graft occlusion.

Vein graft intimal changes: These have been described variously as arterialization, intimal hyperplasia,[5] intimal thickening,[3] intimal fibromuscular hyperplasia or fibrous intimal proliferation.[6] The simple term intimal proliferation is used here. Light and electron microscopic studies have shown that this intimal change is initiated by the proliferation of smooth muscle cells that have emigrated from the media.[8] These cells are capable of synthesizing collagen, elastin and ground substances, resulting in intimal thickening composed of variable amounts of cell elements and extracellular materials. Whether the thickened intima is predominantly cellular or fibrous depends on the time since insertion of the vein graft and many other factors that initiate and perpetuate the proliferative changes.

The pathogenesis of the vein graft intimal changes remains in doubt. However, electron microscopy has demonstrated altered endothelial permeability with the presence of blood constituents in the intima early after graft insertion. It was suggested that plasma factors may reach the media and stimulate smooth muscle cell proliferation.[8] The simple mechanical stretching may also act as a stimulus.[6,8,13] This mechanical stress may be aggravated by distal arterial disease with poor runoff producing a "water-hammer" effect.[6]

Early versus late vein graft changes: Previous pathologic observations suggest that intimal proliferation is rare in the first month after operation. Indeed, the earliest time at which graft obstruction from intimal proliferation has been reported is 4 1/2 months.[6] The intimal changes of the saphenous veins observed in the early group of some of our patients may therefore represent preexisting aging changes. This view is supported by the results of a study of the histologic changes with age in 200 saphenous veins in their normal anatomic position of randomly selected autopsy patients in the 5th and 6th decades of life (J. T. Lie, unpublished data). These veins all showed grade 1 to 2 intimal proliferation. Almost identical degrees of intimal proliferation of a saphenous vein in its anatomic position and a 64 month old graft from the same patient at the time of reoperation are shown in Figure 8. It follows that the intimal changes seen in saphenous veins after aortocoronary bypass surgery must be interpreted with some caution, and preferably compared with the histologic data on the saphenous vein obtained at the time of implantation.

Significant segmental stenoses were rarely observed in our series. It is possible that the severe segmental stenoses previously reported may be related to preexisting lesions of the vein, an organized mural thrombus or trauma to the vein during its removal and implantation.

It is apparent from Table II and Figures 4 to 7 that once grade 2 changes have occurred, vein graft intimal proliferation does not necessarily progress further with time. This is further suggested by the 66 vein grafts studied angiographically between 36 and 75 months. After initial changes had occurred, the severity of intimal proliferation did not undergo significant angiographic progression with the passage of time.

Intimal changes and graft flow: The final change observed angiographically is a uniform reduction in graft caliber by about 30 to 50 percent. Others[14] have also reported this change, but it does not appear to affect graft flow significantly.[15] However, because some degree of intimal proliferation appears to be inevitable, it would seem desirable to use vein grafts that initially are significantly larger than the recipient artery. The long-term angiographic appearance of grafts in our study suggests that use of saphenous veins from the thigh usually results in a final graft lumen size of nearly ideal proportions. This finding contradicts previously raised theoretical objections to the natural disparity in size between the saphenous vein and the recipient coronary artery.

Factors determining graft patency: The reported correlations of early patency with high intraoperative flow rates[9,16,17] suggest that the state of the distal vascular bed may be the single most important determinant of vein graft patency. Saphenous vein grafts attached to the left anterior descending coronary artery (which usually provides good runoff) have shown patency rates in asymptomatic patients comparable with those of internal mammary grafts. However, vein grafts attached to the right or circumflex coronary arteries show significantly lower patency rates.[18] Technical problems in executing anastomoses to small diseased arteries may also be a significant cause of graft failure.

Thus the occurrence of intimal proliferation in vein grafts obviously is not the major reason that the patency rates of most vein grafts are 5 to 15 percent lower than those reported for internal mammary artery grafts.[19,20] Indeed, histologically similar intimal proliferation has been observed in the internal mammary artery grafts.[21] Rather, it appears that to remain patent, saphenous vein grafts require a greater initial flow than internal mammary artery grafts. The latter have been shown to remain patent in the presence of negligible forward flow.[22]

However, once patency is established, the potential maximal flow through saphenous vein grafts is much greater than through internal mammary artery grafts.[23] This may become significant clinically when the distal runoff exceeds the average internal mammary arterial flow of less than 79 ml/min.[20,23]

Clinical implications: The results of our study indicate that the main cause of saphenous vein graft failure in aortocoronary bypass is early thrombosis, mainly in the first 3 postoperative months. The apparent small reduction in patency found 7 to 12 months postoperatively is related to a disproportionately large

number of symptomatic patients restudied at that time interval. Symptomatic patients have previously been shown[18] to have lower graft patency rates.

The saphenous vein remains the most frequently used and most versatile vascular graft available. Early graft failure due to thrombosis may be reduced with further experience in patient and vessel selection and with refinement of techniques. The well maintained late patency rate and the lack of angiographic deterioration of grafts with time suggest that graft occlusion from relentless progression of intimal proliferation alone does not occur commonly enough to inhibit the continued use of the saphenous vein as an aortocoronary bypass graft.

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Chest Pain as a Predictor of Coronary Artery Disease in Patients With Obstructive Aortic Valve Disease

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To clarify the association between chest pain and significant coronary artery disease in patients who have aortic valve disease, 76 consecutive candidates for aortic valve replacement were evaluated prospectively with use of a historical questionnaire and coronary arteriography. Of the 76 patients, 19 (25 percent) had no chest pain, 21 (28 percent) had chest pain that was not typical of angina pectoris and 36 (47 percent) had chest pain typical of angina pectoris. In 18 of 19 patients the absence of chest pain correlated with the absence of coronary artery disease. The single patient without chest pain who had coronary artery disease had evidence of an inferior myocardial infarction in the electrocardiogram. Thus, absence of chest pain and the absence of electrocardiographic evidence of infarction predicted the absence of coronary disease in all cases.

The presence of chest pain did not predict the presence of coronary artery disease, but the more typical the pain of angina pectoris the more likely were patients to have significant coronary artery disease. Of the 21 patients with atypical chest pain, 6 (29 percent) had coronary artery disease, but of the 36 patients with typical angina pectoris 23 (64 percent) had significant coronary artery disease. In addition, when patients with chest pain not typical of angina pectoris also had coronary artery disease, the diseased vessels usually supplied smaller areas of the left ventricle than when the pain was typical of angina pectoris. In 21 of 23 patients (91 percent) with typical angina pectoris and significant coronary artery disease, lesions were present in the left coronary artery. There was no systolic pressure gradient across the aortic valve that excluded the presence of coronary artery disease, although all patients with a calculated aortic valve area of less than 0.4 cm^2 were free of coronary artery disease. Patients with severe left ventricular dysfunction were more likely to have normal coronary arteries.

In patients with aortic valve disease it is important to be confident of the status of the coronary arteries prior to aortic valve replacement because severe narrowing of the coronary ostia or vessels may interfere with adequate myocardial perfusion in the perioperative period and thereby contribute to the mortality and morbidity associated with such surgery.[1,2] In addition, the surgical relief of chest pain may be as dependent on relieving obstruction of the coronary arteries as on relieving left ventricular outflow obstruction. On the other hand, coronary arteriography is associated with a small but definite risk and should not be performed unnecessarily.[3,4] The significance of chest pain in defining coronary arterial obstruction in patients with aortic valve disease is not entirely clear. Although one would expect that patients with both significant, although not necessarily severe, aortic stenosis and coronary artery disease would experience chest pain, this relation has not been clearly defined. Clearer definition is needed in order to define appropriately the indications for coronary arteriography and the role of coronary arterial surgery at the time of aortic valve replacement.

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This study was performed to clarify further the association of chest pain and significant coronary artery disease in patients with obstructive aortic valve disease. A prospective protocol was followed in which all candidates for aortic valve replacement, regardless of the presence or absence of chest pain, were studied with coronary arteriography as part of their hemodynamic evaluation in order to assess the importance of chest pain and the electrocardiogram in predicting the status of the coronary arteries. Our data should provide information that will delineate patients at greatest risk of having coronary artery disease and in whom coronary arteriography would be helpful in the preoperative evaluation.

Patients and Methods

Seventy-six of 79 consecutive men with isolated obstructive aortic valve disease who were candidates for aortic valve replacement were studied. Three patients were excluded because coronary arteriograms were not obtained. The patients ranged in age from 39 to 84 years (mean 57 years). They were treated with digitalis and diuretic agents when necessary and were in optimal clinical condition at the time of the hemodynamic studies. No patient had had previous cardiac surgery.

Evaluation of chest pain: The history of chest pain was evaluated by two methods. First, a clinical history was carefully elicited by at least one of us and subjectively judged to be typical or atypical of angina pectoris. Second, patients were classified according to their response to a prospective questionnaire. Seven characteristics of chest pain were assigned a numerical value so that the total possible value was 12 points. A maximal value of 3 points was assigned to location (central, bilateral, anterior and supramammary) and to factors that aggravated or precipitated chest pain (such as eating, exercise, emotion and exposure to cold temperatures). Two points were possible if the pain was relieved with both rest and nitroglycerin. Less emphasis was placed on quality, duration, radiation of pain and associated symptoms, which were assigned a value of 1 point each when consistent with angina pectoris. Characteristics of chest pain that were not consistent with angina pectoris were assigned no numerical value; for example, an unusual location of pain not relieved with rest or nitroglycerin. Patients whose chest pain was subjectively judged typical of angina pectoris had at least 8 of 12 possible points, whereas those whose pain was judged atypical had fewer than 8 points (Fig. 1). In two patients with 8 points the pain syndrome was arbitrarily categorized as atypical of angina pectoris.

A vectorcardiogram with the Frank lead system was recorded in 70 patients, and a standard 12 lead electrocardiogram was recorded in each patient. Electrocardiographic evidence of coronary artery disease was defined as the presence of myocardial infarction, and isolated repolarization abnormalities were not included as evidence of coronary artery disease.

Cardiac catheterization studies: Right and left heart catheterization was performed in each patient. The systolic gradient across the aortic valve was determined from pressures recorded simultaneously from two Teflon® catheters. The catheter manometer recording system was shown to have a flat (±10 percent) frequency response of at least 50 hertz. Cardiac output was determined as the quotient of the oxygen consumption and the arteriovenous oxygen difference and the result compared with the value obtained with the indicator-dilution technique using Cardiogreen® dye. The mean systolic gradient across the aortic valve was determined from an average of 20 beats. The aortic valve area was calculated according to the formula of Gorlin and Gorlin.[5]

Left ventriculography and ascending aortography were performed in each patient to evaluate the presence of mitral or aortic insufficiency. The degree of aortic insufficiency was estimated from opacification of the left ventricle after aortography. A scale of 0 to 4+ was used: Insufficiency was graded

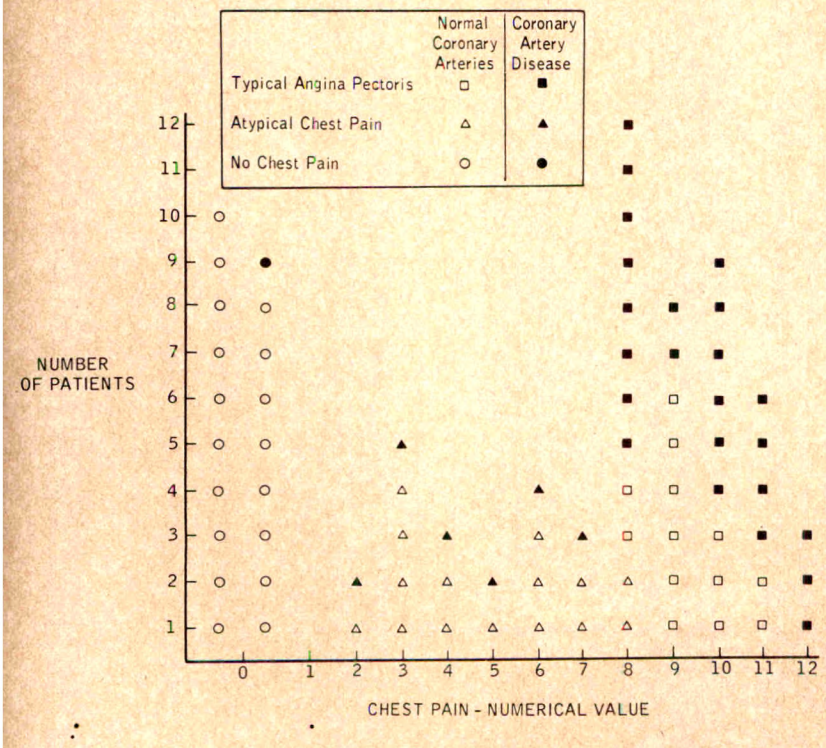


FIGURE 1. Numerical value assigned to the chest pain syndrome on the basis of response to the angina questionnaire. Patients without chest pain are assigned a value of zero. The **open symbols** indicate patients either with no discernible coronary arterial lesion or with lesions obstructing less than 75 percent of luminal diameter.

1+ when the left ventricle was not completely outlined by contrast material, 2+ when there was sufficient regurgitant opacification to outline the left ventricle but less well than the aorta, 3+ when the ventricle was outlined as well as the aorta and 4+ when the ventricle was outlined better than the aorta and when it was also enlarged. The first 3 beats after opacification of the aorta were used. Patients with reflux of contrast material into the left atrium during left ventriculography greater than 1+ on a scale of 0+ to 4+ were excluded as examples of coexistent mitral insufficiency.

Patients were classified into three groups according to the mean systolic pressure gradient and the degree of aortic insufficiency. Group A consisted of 48 patients with predominant aortic stenosis; all had a mean systolic gradient greater than 30 mm Hg or an aortic valve area of less than 1.5 cm^2 and less than grade 2+ aortic insufficiency. Group B consisted of 23 patients with mixed aortic valve disease; all had a mean systolic gradient greater than 29 mm Hg and aortic insufficiency equal to or greater than grade 2+. Group C consisted of five patients with predominant aortic insufficiency (mean systolic gradient 20 mm Hg or less and grade 2+ to 4+ aortic insufficiency. Patients with isolated aortic insufficiency were not included in this study.

Ventricular volumes and ejection fraction were estimated from single plane cineangiograms in the right anterior oblique projection (45°). Ventricular volume was calculated using the area-length method[6–8] and corrected for X-ray magnification.

Coronary arteriograms were obtained in all patients in the right and left oblique projections using the transfemoral percutaneous technique.[9] Cineangiograms were recorded at a rate of 60 frames/sec. Significant obstruction was not judged present unless at least 75 percent of the diameter of the coronary lumen was judged obliterated in at least one view from several projections.

Results

Of the 76 patients, 19 (25 percent) were considered free of chest pain after careful prospective questioning (Fig. 1). Chest pain typical of angina pectoris was present in 36 patients (47 percent), all with 8 or more points on the angina questionnaire. Of the 21 patients (28 percent) judged to have atypical chest pain, all had 8 or fewer points; only 2 patients had 8 points.

There was no significant age difference among these three groups. All patients but one were symptomatic (Table I). In one patient syncope was the sole symptom. Dyspnea and chest pain were commonly associated; 41 of the 58 patients with dyspnea had chest pain. Eighteen of the 19 patients free of chest pain had severe syncope or heart failure, or both. Seventy-five percent of patients were in New York Heart Association functional class III or IV.

Of the 30 patients (40 percent) with significant obstruction of one or more coronary arteries, 13 had significant disease in one coronary artery, 5 in two arteries and 12 in three arteries. Eighteen of the 19 patients without chest pain had no significant lesion. No patient had significant disease of the left main coronary artery.

Correlation of chest pain and coronary arteriographic findings: The presence of chest pain correlated well with the presence of significant coronary artery disease. All but one patient with significant obstruction of one or more coronary arteries had chest pain. Whether the pain was typical or atypical of angina pectoris was not predictive of the presence or absence of coronary artery disease (Fig. 1). Of 36 patients judged to have typical angina pectoris, 23 (64 percent) had significant obstruction in one or more coronary arteries, whereas 13 (36 percent) had normal coronary arteries. Six of 21 patients (29 percent) with atypical chest pain also had significant coronary artery disease (Fig. 2). These six patients had, respectively, 2, 3, 4, 5, 6 and 7 of 12 points on the angina questionnaire. Five of these six patients had significant disease of only the right coronary artery and the sixth had disease of only a small left circumflex vessel. Of patients with typical angina pectoris, only 2 had isolated lesions of the right coronary artery whereas 21 had lesions in the left coronary arterial system. Thus the more typical the chest pain of angina pectoris, the more likely were patients to have disease in the left coronary system.

Of the 19 patients without chest pain only 1 had significant coronary artery disease. That patient had two lesions of the right coronary artery, each obstructing 75 percent of the lumen, and a pattern of inferior myocardial infarction in the electrocardiogram. Of the remaining 18 patients, 1 had minimal irregularity of the wall of the left anterior descending coronary artery, 3

TABLE I

Clinical Data

Chest Pain Syndrome	Age (yr) (mean ± standard error of the mean)	Patients (no.) Total	With Syncope	With Dyspnea
None	60 ± 10	19 (25%)	5 (26.3%)	17 (89.5%)
Atypical of angina pectoris	57 ± 13	21 (27.6%)	6 (28.6%)	13 (61.9%)
Typical of angina pectoris	56 ± 8	36 (47.4%)	11 (30.6%)	28 (77.8%)
Total	57 ± 10	76	22 (28.9%)	58 (76.3%)

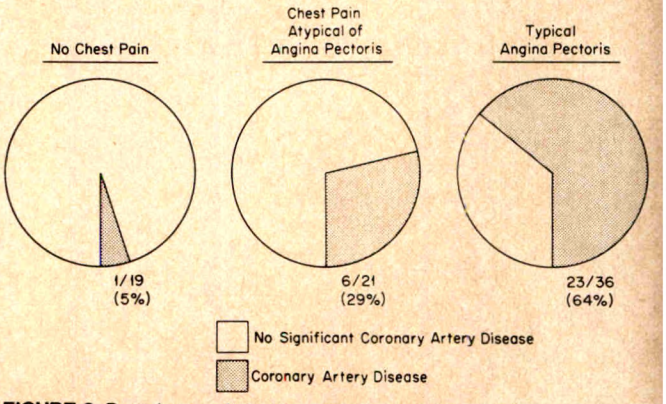


FIGURE 2. Prevalence of significant coronary artery disease in patients with obstructive aortic valve disease according to chest pain syndrome.

TABLE II

Hemodynamic Features of Patients With Obstructive Aortic Valve Disease According to Degree of Aortic Insufficiency (mean ± standard deviation)

	Group A	Group B	Group C
Patients (no.)	48	23	5
Age (yr)	60 ± 10	53 ± 8	47 ± 10
Body surface area (m^2)	1.91 ± 0.18	1.89 ± 0.17	1.93 ± 0.9
Mean systolic gradient (mm Hg)	60.4 ± 22.5	65.0 ± 20.4	14.5 ± 6.4
Aortic valve area (cm^2)	0.63 ± 0.23	0.64 ± 0.26	1.15 ± 0.07
Cardiac output (liters/min)	4.79 ± 1.14	5.52 ± 1.98	5.89 ± 1.42
LV systolic pressure (mm Hg)	191 ± 33	196 ± 30	140 ± 18
LV end-diastolic pressure (mm Hg)	19.8 ± 9.0	19.4 ± 8.9	14.8 ± 13.3
LV ejection fraction (%)	51 ± 22	59 ± 17	68 ± 15

Group A = predominant aortic stenosis (mean systolic pressure gradient 30 mm Hg or more, aortic valve area less than 1.5 cm^2, less than 2+ aortic insufficiency); Group B = mixed aortic valve disease (mean systolic gradient more than 29 mm Hg and 2+ or greater aortic insufficiency); Group C = predominant aortic insufficiency (mean systolic gradient 20 mm Hg or less and 2 to 4+ aortic insufficiency). LV = left ventricular.

had lesions obstructing less than 50 percent of the lumen of that artery, and 14 had no discernible lesion.

Correlation with electrocardiogram: Eighteen patients had electrocardiographic or vectorcardiographic evidence of myocardial infarction. Ten had evidence of inferior wall myocardial infarction. Seven of these 10 patients had significantly obstructive lesions of the right coronary artery, whereas 3 had no evidence of coronary artery disease. Of the three patients with electrocardiographic evidence of inferior infarction but normal coronary arteries, two had no chest pain. The one patient in the entire study without chest pain but with coronary artery disease had electrocardiographic evidence of an inferior wall infarction and significant obstruction of the right coronary artery but a normal left coronary arterial system.

Ten patients had electrocardiographic or vectorcardiographic evidence of anterior myocardial infarction. Two of these 10 patients had neither evidence of coronary artery disease nor chest pain. Each of the eight patients with electrocardiographic evidence of anterior infarction and chest pain had obstructive lesions in the left anterior descending coronary artery. Thus in this study electrocardiographic evidence of anterior wall infarction plus typical angina pectoris was predictive of a significant lesion in the left anterior descending coronary artery.

Correlation of chest pain with severity of aortic stenosis: The frequency of chest pain typical of angina pectoris was similar in Groups A, B and C. Table II indicates the hemodynamic features of these groups. Since the net forward flow and not the actual aortic valve flow was used to calculate aortic valve area, the latter was more likely to be underestimated in patients in Group B (mixed aortic valve disease) than in patients in group A (predominant aortic stenosis). The systemic flow was not significantly greater in group B (5.52 ± 1.98 liters/min) (mean ± standard deviation) than in Group A (4.79 ± 1.14 liters/min) ($P < 0.1$).

In Group A (predominant aortic stenosis), 12 patients had no chest pain and 36 had chest pain (Table III). The mean systolic pressure gradient was greater and the aortic valve area was less in the eight patients with typical angina and no coronary artery disease (70.6 ±

TABLE III

Hemodynamic Data in Patients With Predominant Aortic Stenosis (Group A) (mean ± standard deviation)

	Chest Pain Syndrome					
	None		Atypical of Angina		Typical of Angina	
Patients (no.)	12 (25%)		14 (29.2%)		22 (45.8%)	
Age (yr)	61 ± 10		61 ± 12		58 ± 8	
BSA (m^2)	1.88 ± 0.15		1.88 ± 0.13		1.94 ± 0.21	
MSG (mm Hg)	55.7 ± 18.2		66.2 ± 26.4		59.4 ± 22.1	
AVA (cm^2)	0.59 ± 0.21		0.61 ± 0.21		0.66 ± 0.25	
CO (liters/min)	4.25 ± 0.98		4.80 ± 0.98		5.05 ± 1.28	
LV systolic pressure (mm Hg)	182 ± 21		207 ± 34		185 ± 35	
LV end-diastolic pressure (mm Hg)	20.7 ± 7.6		18.4 ± 7.6		20.1 ± 10.6	
LV ejection fraction (%)	40 ± 21		57 ± 15		52 ± 26	
	No CAD	CAD	No CAD	CAD	No CAD	CAD
Patients (no.)	11 (91.7%)	1 (8.3%)	8 (57.1%)	6 (42.9%)	8 (36.4%)	14 (63.6%)
Age (yr)	61 ±10	68	62 ± 14	60 ± 11	57 ± 9	59 ± 8
BSA (m^2)	1.86 ± 0.15	2.02	1.89 ± 0.10	1.87 ± 0.17	1.90 ± 0.20	1.96 ± 0.22
MSG (mm Hg)	56.9 ± 18.6	42.7	76.0 ± 27.4	53.1 ± 20.1	70.6 ± 12.9	53.0 ± 24.0
AVA (cm^2	0.56 ± 0.20	0.88	0.53 ± 0.18	0.71 ± 0.21	0.49 ± 0.11	0.76 ± 0.26
CO (liters/min)	4.17 ± 0.99	5.11	4.75 ± 0.96	4.88 ± 1.10	4.74 ± 1.04	5.22 ± 1.40
LV systolic pressure (mm Hg)	181 ± 22	191	216 ± 29	194 ± 39	194 ± 22	180 ± 40
LV end-diastolic pressure (mm Hg)	20.1 ± 7.7	27	21.0 ± 8.5	15.0 ± 5.0	21.8 ± 12.3	19.2 ± 9.9
LV ejection fraction (%)	40 ± 21	—	53 ± 17	63 ± 11	44 ± 28	56 ± 24

AVA = aortic valve area; BSA = body surface area; CAD = significant coronary artery disease; CO = cardiac output; LV = left ventricular; MSG = mean systolic pressure gradient.

12.9 mm Hg and 0.49 ± 0.11 cm^2) than in patients with typical angina and coronary artery disease (53.0 ± 24.0 mm Hg and 0.76 ± 0.26 cm^2). This difference was significant for aortic valve area ($P < 0.02$). The mean aortic valve area was also less in the 8 patients with normal coronary arteries and chest pain typical of angina than in the 12 patients without chest pain (0.49 ± 0.11 versus 0.59 ± 0.21), but the difference was not significant ($P < 0.3$). Although there were differences in the mean systolic gradient in Group A among patients without chest pain (55.7 ± 18.2 mm Hg), atypical chest pain (62.2 ± 26.4 mm Hg) and typical angina (59.4 ± 22.1 mm Hg), the differences were not significant. There was no mean systolic gradient that excluded the presence of significant coronary artery disease. For example, a gradient of greater than 100 mm Hg was present in one patient with typical angina pectoris and significant disease in three coronary arteries, but no patient in Group A with a valve area of 0.40 cm^2 or less had significant coronary artery disease (Fig. 3).

Group B consisted of 23 patients with outflow obstruction and moderate to severe aortic insufficiency. There was no significant difference in aortic valve area, mean systolic pressure gradient or left ventricular end-diastolic pressure between patients with and without chest pain. Group B was comparable with Group A in number of patients without and with chest pain. Among patients with typical angina, as many patients had significant coronary artery disease in Group B as in Group A.

Correlation with left ventricular function: The range of left ventricular end-diastolic pressure and ejection fraction was similar in patients without coronary artery disease and in patients with coronary artery disease involving one, two or three vessels (Fig. 4). The left ventricular end-diastolic pressure did not correlate with the ejection fraction ($r = 0.3$). There were 18 patients with an ejection fraction of less than 40 percent and 28 patients with a left ventricular end-diastolic pressure greater than 20 mm Hg. Twelve patients had both an ejection fraction of less than 40 percent and an end-diastolic pressure greater than 20 mm Hg, whereas 34 patients had either or both hemodynamic findings. Of the 18 patients with an ejection fraction of less than 40 percent, 15 (83 percent) had normal coronary arteries; of the remaining 3, and one patient had significant disease in one artery and two patients had significant

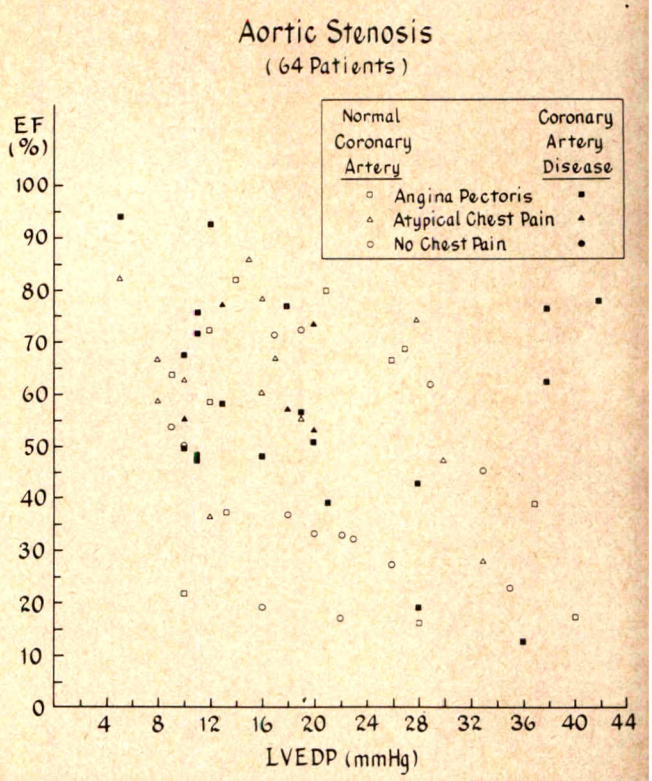


FIGURE 4. Relation between left ventricular end-diastolic pressure (LVEDP) and ejection fraction (EF) in all patients. Symbols as in Figure 1.

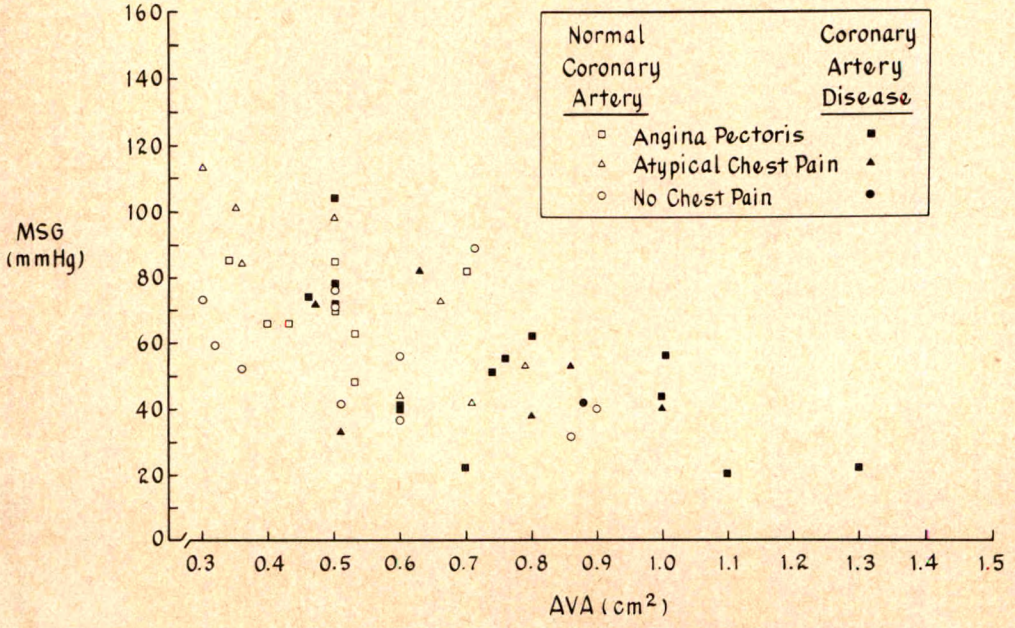


FIGURE 3. Group A (64 patients with predominant aortic stenosis). Relation of the mean systolic pressure gradient across the aortic valve (MSG), aortic valve area (AVA), status of the coronary arteries and chest pain syndrome. **Closed symbols** indicate presence of significant coronary artery disease and **open symbols** indicate patients either with no discernible coronary arterial lesion or with lesions obstructing less than 75 percent of luminal diameter.

disease in three arteries. Thus, whereas patients with chest pain had a high incidence rate of coronary artery disease those without chest pain had a greater incidence of severe ventricular dysfunction. Of the 34 patients with either a left ventricular end-diastolic pressure greater than 20 mm Hg or an ejection fraction of less than 40 percent, or both, 25 (74 percent) had normal coronary arteries and 9 (26 percent) had significant coronary artery disease.

The prevalence rates of both chest pain and dyspnea were similar in each group. The presence or absence of dyspnea in addition to chest pain was not predictive of the presence or absence of coronary artery disease.

Discussion

Predictive value of absence or presence of chest pain in aortic stenosis: In this study the absence of chest pain was the single clinical finding most predictive of normal coronary arteries. With one exception, no patient free of chest pain had significant coronary artery disease. When the findings from the electrocardiogram and vectorcardiogram were added to the history, the presence of normal coronary arteries could be predicted in all cases. Thus, our data suggest that patients without chest pain or electrocardiographic evidence of infarction are likely to be free of significant coronary artery disease and that coronary arteriography should yield minimal additional data. This finding may be of considerable importance in selecting diagnostic studies of greatest yield for patients with clinically severe aortic stenosis and left ventricular failure. These data are in agreement with findings in several previous reports.[10–12]

When patients complained of chest pain, whether typical of angina pectoris or not, one could not predict the presence or absence of coronary artery disease even when other clinical or laboratory findings were included. Patients with atypical chest pain were more likely to have isolated disease of the right coronary artery, whereas those with typical angina pectoris were more likely to have disease of the left coronary arterial system. Fifty-eight percent of all patients with typical angina pectoris had significant obstructive lesions of the left coronary arterial system. Ninety-one percent of patients with both typical angina pectoris and coronary artery disease had significant lesions in the left coronary system. A continuum is thereby established: the more characteristic the chest pain of angina pectoris, the greater the likelihood of severe coronary artery disease; the less characteristic the chest pain of angina pectoris, the greater the likelihood of mild or absent coronary artery disease. The absence of chest pain nearly always excludes the presence of coronary artery disease.

The electrocardiogram and vectorcardiogram generally added little to the history of chest pain in predicting the anatomic status of the coronary arteries. In one exceptional case, a patient who was free of chest pain had significant coronary artery disease. In this case the electrocardiogram revealed an inferior myocardial infarction and coronary arteriography revealed coronary artery disease isolated to the proximal and distal right coronary artery.

The absence of coronary artery disease in our patients free of chest pain was not biased by selection of patients with a low prevalence rate of coronary artery disease; in fact, this rate (39 percent) was greater than that reported in several studies.[10–14] This is in part explained by our study group, which was composed of adult men in whom symptoms from obstructive aortic valve disease and coronary artery disease are likely to occur at a similar age. Similarly, the prevalence rate of patients with three vessel coronary disease (16 percent of all patients) was equal to or greater than that in most studies,[10,14] and the frequency of coronary artery disease in our patients with angina pectoris (64 percent) was equal to or greater than that reported in several studies.[15]

Significance of severity of aortic valve obstruction: In patients with aortic stenosis, blood supply, especially to the subendocardium, may be restricted by an increase in left ventricular diastolic pressure, a decrease in diastolic filling period and an increase in intramyocardial tension, which may constrict the intramyocardial arteries.[16–18] Coronary artery disease would further restrict blood supply to the myocardium. It seems reasonable therefore that patients with very severe obstruction at the aortic valve would have less coronary artery disease, and, this was generally true in that Group A patients with an aortic valve area of less than 0.40 cm^2 were free of coronary artery disease. However, eight patients with a mean systolic gradient across the aortic valve of more than 70 mm Hg also had severe coronary artery disease. Thus, a large systolic gradient would not preclude the need to perform coronary arteriography to assess the status of the coronary arteries. On the other hand, all patients with an aortic valve area of 1.0 c cm^2 or greater and angina pectoris had significant coronary artery disease. The circumstances that may provide for the simultaneous development of severe aortic obstruction and coronary artery disease in some patients is not clear. A different rate of development of each process and, in some cases, physical inactivity may allow them to reach similar degrees of severity at the same time.

Significance of left ventricular dysfunction: Our results indicated that approximately two thirds of patients with angina pectoris had significant coronary artery disease, whereas patients with a decreased ejection fraction were more likely to have normal coronary arteries. It seems reasonable that longevity would be seriously jeopardized in patients with both severe left ventricular dysfunction and advanced coronary artery disease and few such patients would then be expected to be available for this study. That aortic stenosis may lead to ventricular ischemia, dysfunction, fibrosis and infarction with normal coronary arteries is well established.[16–19] Why some patients with normal coronary arteries and severely obstructive aortic valve lesions have angina pectoris and others have ventricular dysfunction is not clear. In aortic stenosis, angina pectoris may result not only from an increased demand but also from an inability to increase coronary blood flow sufficiently.[16–18] In such patients repeated episodes of sub-

endocardial ischemia may then lead to ventricular fibrosis and dysfunction without angina pectoris.[17,19] It is well recognized that severe ischemic heart disease including myocardial infarction may occur in the absence of angina pectoris. Perhaps patients with ventricular dysfunction and normal coronary arteries are similar to patients with ischemic heart disease and an elevated pain threshold.

Factors accounting for differences from previously reported data: Results of previous studies dealing with the value of chest pain in predicting the presence of coronary artery disease have been inconclusive.[10–15,20,21] Some of these differences may be due to variation in gathering historical information and to placing value judgments on whether the pain is typical of angina pectoris.[14] In our study, the response to a prospective angina questionnaire ensured uniformity and objectivity in gathering historical information.

In addition, differences in the prevalence of coronary artery disease in patients with aortic stenosis may be due to differences in the interpretation of what constitutes a significant lesion. Several models have indicated that approximately 75 percent obstruction is necessary before flow is seriously impeded.[22,23] Clinical experience in male patients with a normal aortic valve indicates a good correlation among symptoms, stress electrocardiogram and the degree of obstruction by coronary arteriography.[24] It is difficult, however, to be certain that similar degrees of coronary obstruction carry the same significance in patients with a normal aortic valve and those with aortic valve disease, who have increased myocardial oxygen needs.[23] In spite of these differences, all but one of our patients without chest pain had no lesion obstructing either 75 or 50 percent of the lumen.

Interobserver variation in estimating the degree of obstruction of the coronary arterial lumen may also account for some of the differences between investigators.[25] We attempted to reduce such bias by having the coronary arteriograms reviewed by at least three persons. At least one observer was not familiar with the clinical history obtained at the time of reviewing the coronary arteriograms.

Acknowledgment

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Dynamic Changes in Left Ventricular Wall Thickness and Their Use in Analyzing Cardiac Function in the Conscious Dog

A Study Based on a Modified Ultrasonic Technique

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The thickness of the left ventricular free wall and internal chamber diameter were continuously measured by pairs of ultrasonic crystals together with left ventricular pressure in normal conscious dogs. During the resting state, wall thickness decreased abruptly with the onset of atrial contraction from 10.5 mm to an average end-diastolic value of 9.8 mm. In contrast to most previous studies, there was no change in wall thickness during isovolumic systole, and with ejection the wall thickened by 31.3 percent of end-diastolic wall thickness. Atrial pacing, phenylephrine, isoproterenol and propranolol produced significant changes in chamber size with reciprocal changes in wall thickness. In addition, changes in the extent and velocity of left ventricular chamber shortening in the minor equator were associated with comparable reciprocal changes in the extent and velocity of free wall thickening (correlation coefficients 0.97 to 0.99). During acute coronary occlusion, progressive reductions in the extent and velocity of regional wall shortening with partial ischemia were associated with comparable changes in systolic wall thickening characteristics (r = 0.96 and 0.95), and holosystolic elongation in fully ischemic areas was associated with holosystolic wall thinning. During chronic pressure overload, despite wall thickening, the relation between chamber shortening and wall thickening were retained and direct computation of dynamic wall stress variations was possible. These measurements allowed precise definition of the dynamics of the left ventricular wall during normal and abnormal cardiac states. The demonstration that in the absence of regional dysfunction analysis of wall thickness in a single region of ventricular free wall can be used to describe myocardial and overall left ventricular function, as well as regional function in the presence of ischemia, constitutes a new approach to the assessment of cardiac function that has potential for echocardiographic applications.

The importance of wall thickness in evaluating the mechanical performance of the left ventricle was recognized by Woods[1] in 1892 in his attempt to apply the law of Laplace to the calculation of cardiac wall tension, and Burton[2] later emphasized the relation between the shape and size of the ventricle and the performance of the heart as a pump. Various techniques have been developed in an effort to obtain quantitative information concerning changes in wall thickness during the cardiac cycle. These have included radiographic methods with contrast visualization[3–10] or metallic objects attached to the myocardium,[11,12] mercury resistance gauges,[13] specially devised dimension transducers[14–16] and echocardiography.[17–23] However, most of these approaches have disadvantages. With radiographic contrast methods, it is difficult to demarcate the boundary between the ventricular wall and the contrast material; the measurement of distances between radiopaque markers placed on the ventricle is influenced by the rotation of the heart and X-ray distortion, and the frequency of sampling is limited by filming rate; most of the transducers devised for measurement of wall thickness

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have been attached mechanically across the ventricular wall, which may result in distortion of wall motion. Echocardiography with transmitted ultrasound lacks some of these problems, but it is potentially subject to difficulties introduced by cardiac rotation, the need to use specific transducer locations and angles, and inability to obtain satisfactory tracings in some subjects. These problems, and the wide variety of methods used to study dynamic changes of wall thickness, have produced lack of agreement in reported data.

The purpose of this study was to apply a recently developed ultrasonic technique for measuring left ventricular regional dimensions[24–28] to a systematic investigation of dynamic wall thickness changes in the conscious dog. Wall thickness was measured together with the internal diameter of the left ventricular chamber in order to describe precisely the phasic pattern of changes in wall thickness during the normal cardiac cycle. In addition, we sought to define the effects of alterations in overall and regional left ventricular function on the dynamic characteristics of the wall to demonstrate, if possible, the usefulness of changes in wall thickness in assessing myocardial function.

Our findings document the dynamics of left ventricular wall thickening under several conditions and show that a single transmural area of the left ventricular free wall can be used to reflect myocardial function and overall left ventricular dynamics in the absence of regional dysfunction; in ischemic disease, the dynamics of regional wall thickening accurately mirror the circumferential shortening characteristics of the adjacent subendocardial segment. These findings offer a new approach to the analysis of ventricular and regional myocardial function which has important implications for the application of reflected ultrasound to these purposes.

Methods

Instrumentation: Fifteen mongrel dogs weighing 22 to 32 kg (average 26.9 kg) underwent right thoracotomy in the fourth intercostal space under sodium pentobarbital anesthesia (25 mg/kg body weight intravenously). The pericardium was widely opened. A high fidelity micromanometer (Konigsberg P-22) was inserted into the left ventricular chamber through a stab incision at the ventricular apex, and a Silastic® catheter was positioned in the left ventricle to obtain zero pressure reference and calibrations. A pair of crystals was placed to measure continuously left ventricular wall thickness. The subendocardial crystal of this pair (1.5 mm in diameter, with miniature flaccid stainless steel connecting wires[27]) was held at the tip of a small teflon tube and advanced diagonally to a site close to the endocardium through a tunnel created by an 18 gauge hypodermic needle. The teflon tubing was then withdrawn, leaving the small transducer near the subendocardium facing outward. The epicardial crystal (5 mm diameter disc) was sutured in place at the site where the ultrasonic transit time was shortest between the two crystals. This technique allowed placement of the crystals across the left ventricular free wall without damage to the intervening tissue.[26] An additional pair of ultrasonic crystals (5 megahertz piezoelectric discs, each 5 mm in diameter) was positioned through small stab incisions at the anterior and posterior endocardial surfaces of the left ventricular cavity, near the minor equator, for measurement of internal chamber diameter. An inflatable cuff was also positioned on the ascending aorta at the time of operation.[26] A pacing wire was attached to the right atrial appendage to control the heart rate during each study.

In an additional nine dogs the left circumflex coronary artery was dissected free near its origin, and a hydraulic cuff was placed around it.[26] In each dog, two pairs of ultrasonic crystals were inserted at two sites: in a normally perfused area, and in an area to be rendered ischemic by inflation of the cuff. One crystal pair at each site was implanted subendocardially in the left ventricular wall in a circumferential plane for the measurement of segment length,[28] and the other pair was positioned for measurement of wall thickness.

Measurements: Hemodynamic measurements were recorded during each experiment on a forced-ink oscillograph and stored on magnetic tape for later playback and computation, as described elsewhere.[26,27] The details of the ultrasonic technique used for continuous measurements of dimensions have been previously described.[28,29] Briefly, the transit time of pulses of ultrasound traversing the myocardium intervening between the crystals is measured at a high repetition rate to provide an effectively continuous measurement of the length of myocardium separating the crystals. During each experiment, the measured transit time was calibrated against a standard crystal-controlled oscillator and was converted to distance using a velocity of sound of 1.5 mm/μsec.

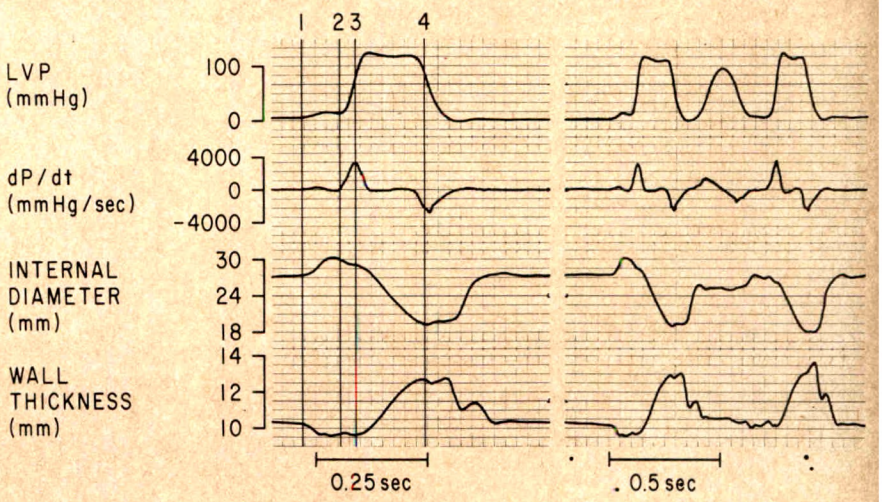


FIGURE 1. Left panel, original tracing showing normal wave forms in a conscious dog in the basal resting state. **From top to bottom:** left ventricular pressure (LVP) and its first derivative (dP/dt), internal left ventricular diameter and left ventricular wall thickness. **Vertical lines** show: (1) the point just prior to onset of atrial contraction, (2) end-diastole, (3) the onset of ejection, and (4) end-ejection. Note the lack of change in wall thickness during isovolumetric systole. **Right panel,** the lack of wall thickening is also evident in the ventricular premature contraction, which is isovolumetric.

TABLE I

Summary of Data (averages ± standard error of the mean)

	Control	Pacing				Control	PE	Control	Iso	Prop	Control	Ao Constr
Heart rate (beat/min)	82.7 ± 2.9	100	120	140	160	89 ± 6	74 ± 11	79	130	72	102 ± 5	101 ± 5
ET (msec)	166 ± 4	160 ± 4	152 ± 3	142 ± 3	137 ± 3	162 ± 6	187 ± 10†	174	148	192	166 ± 5	178 ± 5
LVEDP (mm Hg)	13.1 ± 0.9	11.3 ± 0.6	8.2 ± 0.8	6.3 ± 0.5	5.2 ± 0.5	13.0 ± 1.6	33.2 ± 4.3*	12	8	15	12.7 ± 1.4	18.2 ± 2.5*
LVP (mm Hg)	137 ± 5	141 ± 5	144 ± 5	146 ± 5	145 ± 5	139 ± 10	208 ± 18*	144	148	138	150 ± 4	215 ± 9‡
LVID (mm)												
1	29.2 ± 1.5	28.4 ± 1.6	28.5 ± 1.6	26.8 ± 2.2		28.4 ± 1.8	32.0 ± 1.5†	25.3	23.4	25.8	30.3 ± 2.6	31.1 ± 2.8
2	31.1 ± 1.5	30.2 ± 1.6	29.4 ± 1.6	28.4 ± 1.6	27.6 ± 1.8	30.2 ± 1.7	32.6 ± 1.5*	26.7	25.7	27.2	32.4 ± 2.7	32.5 ± 2.8
3	30.5 ± 1.5	29.8 ± 1.6	28.9 ± 1.6	27.8 ± 1.6	27.1 ± 1.6	29.1 ± 1.6	31.4 ± 1.6	26.2	25.3	26.8	31.8 ± 2.9	31.8 ± 2.8
4	21.7 ± 1.6	21.5 ± 1.6	21.2 ± 1.6	20.7 ± 1.6	20.5 ± 1.7	20.4 ± 1.8	24.3 ± 1.7*	17.5	15.6	18.4	23.3 ± 3.0	23.7 ± 3.5
LVWTh (mm)												
1	10.5 ± 0.5	10.6 ± 0.6	10.8 ± 0.5	10.5 ± 0.7		10.5 ± 0.8	9.7 ± 0.9*	9.2	9.5	9.1	10.7 ± 0.6	11.9 ± 0.6‡
2	9.8 ± 0.4	10.1 ± 0.4	10.3 ± 0.5	10.5 ± 0.5	10.8 ± 0.6	10.0 ± 0.8	9.4 ± 0.9*	8.9	9.1	8.8	10.2 ± 0.5	11.3 ± 0.6‡
3	9.9 ± 0.4	10.1 ± 0.4	10.3 ± 0.4	10.4 ± 0.5	10.7 ± 0.5	10.1 ± 0.7	9.6 ± 0.8	8.9	9.1	8.8	10.3 ± 0.5	11.4 ± 0.6‡
4	12.9 ± 0.6	13.0 ± 0.6	13.0 ± 0.6	13.1 ± 0.6	13.3 ± 0.7	13.1 ± 1.1	11.6 ± 1.0*	11.2	11.8	10.8	13.2 ± 0.7	14.4 ± 0.8
ΔL (mm)	9.4 ± 0.4	8.7 ± 0.4	8.1 ± 0.4	7.6 ± 0.4	7.1 ± 0.6	9.8 ± 0.7	8.3 ± 0.9*	9.2	10.1	8.7	9.1 ± 0.6	8.9 ± 0.7
100ΔL/EDD (%)	31.3 ± 1.8	29.7 ± 1.8	28.4 ± 1.7	28.0 ± 1.8	26.2 ± 2.1	33.0 ± 3.0	25.6 ± 2.7*	34.7	40.8	32.2	29.6 ± 3.5	28.7 ± 3.6
V_{ID} (diameter/sec)	1.89 ± 0.11	1.87 ± 0.12	1.89 ± 0.12	1.97 ± 0.14	1.94 ± 0.17	2.04 ± 0.19	1.38 ± 0.17†	1.99	2.82	1.60	1.77 ± 0.19	1.61 ± 0.21
ΔW (mm)	3.1 ± 0.3	3.0 ± 0.3	2.7 ± 0.2	2.6 ± 0.2	2.5 ± 0.2	3.2 ± 0.5	2.2 ± 0.3*	2.3	2.7	2.1	3.0 ± 0.3	3.1 ± 0.4
100ΔW/EDWTh (%)	31.9 ± 2.9	29.7 ± 2.6	26.2 ± 2.1	23.3 ± 1.6	22.8 ± 1.6	32.3 ± 4.8	25.0 ± 3.9	25.5	30.2	23.7	29.5 ± 2.2	27.5 ± 3.0
V_{WTh} (thickness/sec)	1.93 ± 0.17	1.88 ± 0.18	1.75 ± 0.15	1.72 ± 0.14	1.68 ± 0.13	1.97 ± 0.26	1.34 ± 0.21*	1.49	2.08	1.24	1.78 ± 0.11	1.55 ± 0.17
CSA (%)	100.3 ± 0.4	100	100.5 ± 0.4	100.6 ± 0.7	101.7 ± 1.1	100.6 ± 0.9	98.8 ± 1.9	100	99.7	99.0	100	114.3 ± 1.3
Peak WSt (× 10^3 dynes per cm^2)											140 ± 11	156 ± 14

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ are by comparison with control values. P values are not presented for isoproterenol and propranolol studies because there were only three dogs in each group. 1 = value before atrial contraction; 2 = end-diastolic value; 3 = value at peak dP/dt; 4 = end-systolic value.

Ao Constr = after sustained aortic constriction for an average of 18 days; CSA = cross-sectional area (expressed as percent of the value at a heart rate of 100 beats/min); ΔL = change in left ventricular internal diameter during systole; ΔW = change in left ventricular wall thickness during systole; ET = ejection time; Iso = isoproterenol; LVEDP = left ventricular end-diastolic pressure; LVID = left ventricular internal diameter; LVP = left ventricular peak pressure; LVWTh = left ventricular wall thickness; 100ΔL/EDD = percent left ventricular shortening; 100ΔW/EDWTh = percent wall thickening; PE = phenylephrine; Prop = propranolol; V_{ID} = internal diameter shortening rate normalized by end-diastolic diameter (diameter/sec); V_{WTh} = wall thickening rate normalized by end-diastolic wall thickness (thickness/sec); WSt = wall stress.

The following four points within the cardiac cycle were identified for analyses (Fig. 1): (1) The point just before atrial contraction, identified by a small initial increase in the first derivative of left ventricular pressure (dP/dt); (2) end-diastole, the point just before onset of rapid left ventricular pressure increase, where dP/dt is zero; (3) the onset of ventricular ejection, identified by peak dP/dt.[30] (This definition was confirmed by observations in three dogs subjected to retrograde aortic catheterization which showed that the onset of pressure increase in the aorta immediately above the aortic valve coincided with peak dP/dt both before and during aortic constriction; as shown in other investigations [Fig. 1], a reduction in minor equator diameter due to change in shape can occur before aortic valve opening); (4) the end of ventricular ejection, identified as the nadir of the ventricular diameter tracing.

An index of left ventricular muscle mass was estimated by determining the cross-sectional area of the left ventricular wall in a transverse plane using end-diastolic wall thickness and chamber diameter to calculate internal chamber area and total area.[26] The excursions of wall thickness and internal diameter from end-diastole to the end of ejection were normalized by dividing by the end-diastolic value and was expressed as percent thickening and percent shortening, respectively. The mean velocities of wall thickening (mean V_{WTh}) and of internal diameter shortening (mean V_{ID}) were obtained by dividing the stroke excursion by the ejection period (defined as the time from peak dP/dt to the nadir of the diameter tracing), corrected for end-diastolic values.

Instantaneous wall stress, expressed as $WSt = P \times D/4 WTh$ (where P is pressure, D is internal diameter, and WTh is wall thickness), was calculated with an analog multiplier and a divider. X-Y plots of the wall thickness-internal diameter relation throughout the cardiac cycle were obtained using an oscilloscope.

Certain limitations of this method for measuring wall thickness should be noted. The dimension signal obtained from one portion of the ventricle is assumed to be representative of the muscle of the whole left ventricle. Obviously, in the presence of regional dysfunction, local and overall function cannot be equated even though the method can be applied to study segmental contractile responses.[31] The blind placement of the subendocardial crystal leads occasionally to its displacement from an axis perpendicular to the plane tangential to the epicardial crystal, or to a position not precisely at the endocardial surface. The crystals at post-mortem examination were located appropriately across the ventricular free wall in all 15 preparations, although the endocardial crystal was positioned 30 percent of the distance from the endocardial surface in two dogs. We have previously shown[26] that in most instances it is possible to place the crystals within 1 or 2 mm of the endocardium. Finally, lateral movement of the thickness crystals could be caused by shearing motion between epicardial and endocardial surfaces and is indistinguishable from radial motion by this unidimensional measuring technique. However, measurement of phasic translation of epicardial and endocardial surfaces using multiple transducers and triangulation showed the lateral shearing motion to be small.[32] Thus, although the dimensions obtained in this study did not always represent absolute wall thickness from an anatomic point of view, it seems likely that they are reliable for the evaluation of relative dynamic changes during the cardiac cycle and for assessment of interventions in the same animal.

Protocol: After recovery from operation, at least 10 days postoperatively, the studies were performed with the dogs lying quietly awake on the floor. Data were obtained during spontaneous sinus rhythm and atrial pacing; pacing frequencies were increased stepwise from 100 to 160 beats/min and analyses were made when a steady state was achieved. Seven to ten successive beats were averaged at each step. In five dogs, bolus injections of phenylephrine (0.01 mg) were given and recordings made continuously until a steady state response was reached, values being recorded in a series of beats as the systemic pressure increased and also during the steady state. In three dogs, isoproterenol (0.1 μg/kg per min) was infused until a steady state was obtained in which peak dP/dt was increased by 30 to 50 percent. After sufficient time had elapsed for complete recovery to control values, propranolol (1 mg/kg) was injected intravenously and measurements were made five minutes later. In some experiments, after these control studies, the aortic cuff was inflated to produce chronic aortic constriction and the constriction was maintained for an average of 18 days. The steady state responses to this intervention are reported elsewhere[26] and representative dynamic changes in wall stress will be illustrated herein.

Statistical analyses: The percent values relative to control values of end-diastolic dimensions and dynamic changes in wall thickness and chamber diameter were averaged in groups of dogs at the spontaneous sinus rate and at each paced rate; linear correlations between these variables were then calculated using the grouped data. In response to phenylephrine or to acute coronary occlusion, the sequential changes in the dynamics of wall thickness and diameter or segment length were expressed as percent of control in each dog and plotted beat to beat after the intervention until a steady state was achieved; linear regression analysis was then performed using all points. In three dogs in which positive and negative inotropic interventions were used, values in the steady state were averaged and the percent of these values relative to average control levels was analyzed. A paired *t* test was used for other statistical analyses of several variables in the steady state.

Results

Changes in wall thickness during the normal cardiac cycle (Fig. 1, Table I): In 15 normal conscious dogs in the basal state, wall thickness decreased during atrial contraction by an average of 7 percent, from 10.5 mm to a value of 9.8 mm during end-diastole. Wall thickness then remained unchanged during isovolumic left ventricular systole despite a slight but significant decrease in chamber diameter (31.1 to 30.5 mm). Also, during ventricular premature beats without shortening (assumed to be isovolumic beats) the wall did not thicken during systole. During left ventricular ejection the wall thickened to an average of 31.9 percent above the end-diastolic value. Concomitantly, internal chamber diameter decreased by 31.3 percent of the end-diastolic value. The average of the mean wall thickening velocities (mean V_{WTh}) was 1.93 wall thickness/sec (range 0.91 to 3.23), a value similar to the average of the mean shortening velocities (mean V_{ID}) of the cavity internal diameter of 1.89 diameters/sec (range 1.07 to 2.63). With the onset of diastole, there was rapid thinning of the wall followed by slower but continuous further thinning during slow filling.

A consistent linear relation between the changing internal diameter and wall thickening during systole was evident during a wide variety of interventions (Fig. 2); the diastolic relation was far more variable, presumably because of regional variations in relaxation.

Effects of changing heart rate: With stepwise increases in heart rate induced by right atrial pacing, there

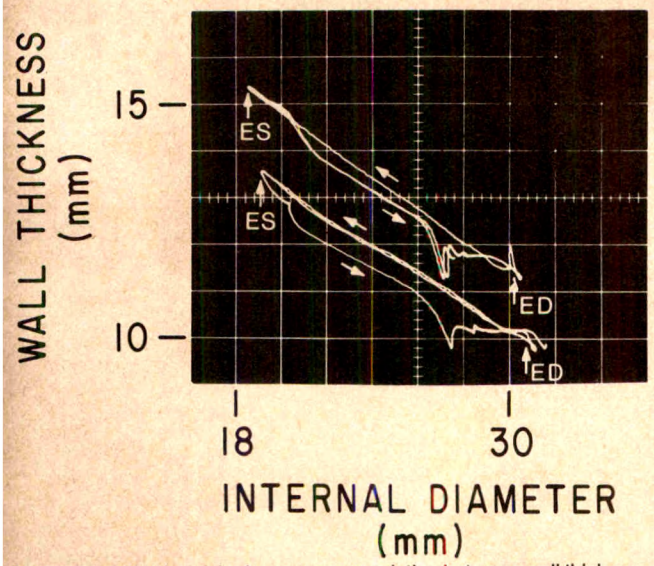


FIGURE 2. X-Y plot of the instantaneous relation between wall thickness and internal diameter during representative cardiac cycles. The **lower loop** was obtained from a control study in a normal dog and the **upper loop** from the same dog after chronic hypertrophy had been induced by aortic constriction. Heart rate was matched in each recording. End-diastolic (ED) and end-systolic (ES) points are shown by **vertical arrows.** Direct linear relations were demonstrated during systole in each loop **(arrows directed to left).** The upward shift of the loop indicates the increased muscle mass of the hypertrophied ventricle.

was a progressive increase in end-diastolic wall thickness associated with decreases of end-diastolic internal chamber diameter (Fig. 3A). At rates higher than 160 beats/min, atrial systole was no longer apparent. Calculated wall cross-sectional area remained constant at the different heart rates (Table I). The extent of thickening during systole was diminished with increasing heart rate and was associated with comparable reductions in the extent of shortening of chamber diameter. Despite wide scatter in the absolute data because of absolute differences among individual dogs, the average percent of control level of the excursions of wall thickness was linearly related to that of internal diameter (Fig. 3B). However, the slope became steeper when these data were normalized for end-diastolic values to permit comparison of function of ventricles of different size because values for end-diastolic diameter and end-diastolic wall thickness moved in opposite directions (Fig. 3C).

Effects of phenylephrine: Heart rate at steady state after infusion of phenylephrine was not significantly slower than the control value (Table I). Peak left ventricular systolic pressure and left ventricular end-diastolic pressure were significantly elevated from 139 to 208 mm Hg and from 13 to 33 mm Hg, respectively. There was significant chamber dilatation, left ventric-

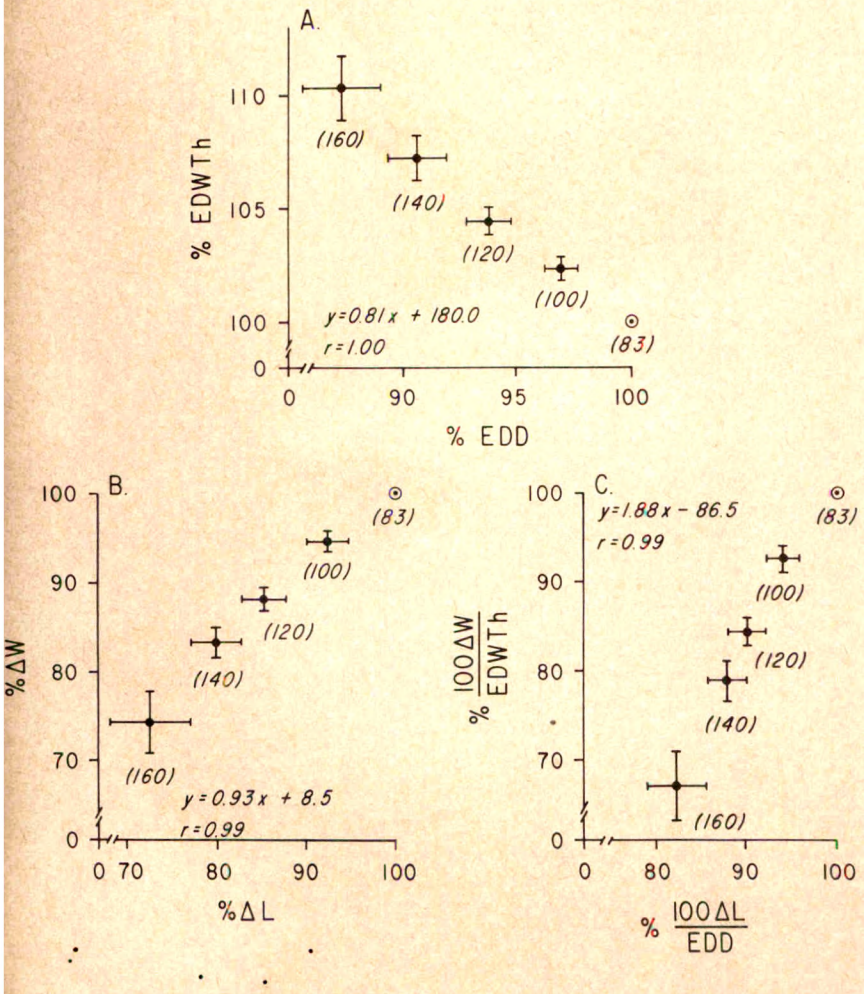


FIGURE 3. Effects of stepwise increases in heart rate (in beats/min, indicated in parentheses below each point) on left ventricular wall thickness and internal diameter. **A,** correlation at a basal heart rate of 83 beats/min **(open circle)** between the percent of the control value of end-diastolic wall thickness (EDWTh) and that of end-diastolic diameter (EDD) (mean ± standard error) in 15 dogs. **B,** correlation between the percent of control value of the extent of wall thickening (ΔW) and that of the extent of internal diameter shortening (ΔL). **C,** correlation between the percent of the control value of the extent of thickening (ΔW) normalized for end-diastolic wall thickness (EDWTh) × 100 and extent of internal diameter shortening similarly normalized for end-diastolic diameter (EDD).

ular end-diastolic diameter increasing from 30.2 to 32.6 mm; end-diastolic wall thickness decreased from 10.0 to 9.4 mm. There was no significant change in calculated cross-sectional area.

Phenylephrine-induced changes relative to control values for normalized stroke excursion of wall thickening versus that of internal chamber shortening (Fig. 4A) and mean wall thickening velocity versus mean shortening velocity (Fig. 4B) were plotted. A series of beats were analyzed during the early course of the response to phenylephrine in each of the five dogs. Nearly linear functions relating the averages of these variables were obtained.

Effects of inotropic interventions (Table I): *With infusion of isoproterenol,* heart rate increased from 76 to 130 beats/min. Left ventricular end-diastolic pressure was decreased from 12 to 8 mm Hg without significant change in left ventricular systolic pressure, and peak dP/dt increased from 3,760 to 5,120 mm Hg/sec. Left ventricular end-diastolic diameter decreased significantly from 26.7 to 25.7 mm with a marked increase in shortening. There was a reciprocal increase in left ventricular end-diastolic wall thickness from 8.9 to 9.1 mm together with increased systolic thickening; cross-sectional area remained unchanged. Percent shortening and mean shortening velocity were augmented by 18 and 42 percent, respectively, over control values, and wall thickening increased comparably; percent wall thickening and mean wall thickening velocity were increased by 18 and 40 percent, respectively, above control values.

After propranolol, heart rate decreased by 22 beats/min, left ventricular end-diastolic pressure was elevated, left ventricular systolic pressure was decreased, and peak dP/dt was reduced to 3,300 mm Hg/sec. Left ventricular end-diastolic diameter was increased to 27.2 mm with concomitant wall thinning; cross-sectional area was unchanged. There was a 7 percent decrease in percent shortening and 17 percent decrease in mean shortening velocity, and wall thickening was equally depressed by administration of propranolol; percent thickening was reduced by 7 percent and mean wall thickening velocity by 16 percent.

The correlations between normalized wall thickening and diameter shortening were compared (Fig. 4C) and between velocities of wall thickening and internal diameter shortening were established (Fig. 4D) in response to isoproterenol and propranolol. The relations between these changes are linear.

The effects of acute coronary occlusion (Fig. 5): Because coronary occlusion is known to induce a prompt and extreme transition from normal circumferential shortening to passive elongation of regional myocardial segments deprived of blood supply,[27,28] this intervention was used to determine the relation between circumferential segment function and wall thickness during

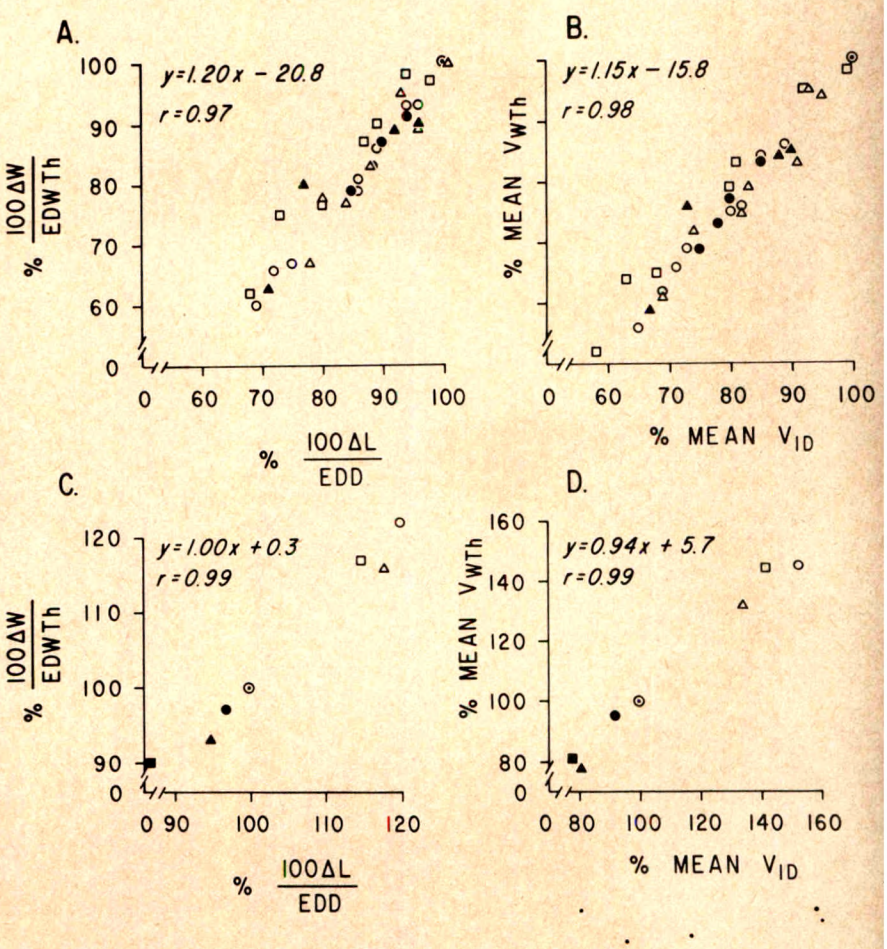


FIGURE 4. Changes in wall thickness and chamber diameter during responses to phenylephrine and isoproterenol. (Comparisons of percent of control value of normalized wall thickening and of the extent of shortening are represented as in Figure 3C.) The relation between percent of control values for mean velocity of wall thickening (mean V_{WTh}) and for velocity of internal diameter shortening (mean V_{ID}) are also shown. **A and B,** sequential beats during the early course of the responses to phenylephrine in five dogs. **Each set of symbols** indicates a series of beats in a different dog. **Circles with dots** represents average control values. **C and D,** average responses to isoproterenol and to propranolol. Average control values are indicated by the **circles with dots. Each symbol** indicates a different dog. Data were obtained by averaging several beats during the steady state after the drug effect was maximal and they are expressed as percent relative to averaged control values, the set of **open symbols** representing responses to isoproterenol (three dogs) and the **closed symbols** responses to propranolol (three dogs).

these extreme modifications of regional myocardial contraction. After coronary occlusion, ischemic zone segment lengths showed gradual reduction of systolic shortening accompanied by a progressive increase in end-diastolic length during the first 20 seconds. Then, early systolic expansion developed followed by protodiastolic shortening; complete holosystolic expansion appeared at 1 1/2 to 2 minutes. Changes in wall thickness reflected these alterations of segment lengths. Diastolic wall thickness in the ischemic segment was reduced immediately after coronary occlusion; wall thickening during systole became gradually reduced and finally was replaced by systolic thinning. In the normal control segments, transient increases of shortening and enhanced systolic wall thickening were seen 5 to 20 seconds after coronary occlusion; subsequently, end-diastolic lengths gradually increased and shortening was augmented. These changes were associated with a concomitant change in end-diastolic wall thickness and wall thickening during systole.

The changes in normalized segment shortening were linearly related to normalized wall thickening during the early course of acute coronary occlusion in both normal and ischemic segments (Fig. 6A). Segment lengths and wall thickening and thinning were similarly related. The changes in mean shortening velocity and mean wall thickening velocity were also linearly related (Fig. 6B).

Effects of chronic aortic constriction and hypertrophy (Fig. 7): Left ventricular pressure, internal diameter, wall thickness and analog computation of wall stress were recorded from a representative animal subjected to aortic constriction to produce increased left ventricular pressure sustained for 21 days. In the control recording, peak wall stress was attained early in ejection before any significant increase in wall thickness; stress

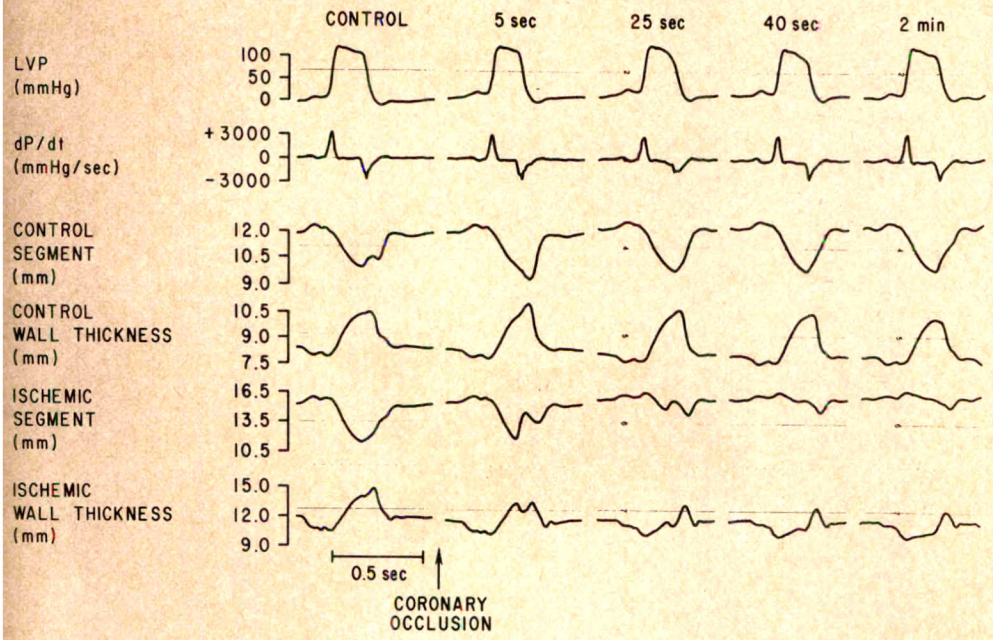


FIGURE 5. Effects of acute coronary occlusion on left ventricular pressure (LVP), its first derivative (dP/dt), segment length and wall thickness in control and ischemic areas. The time of occlusion is indicated by the **arrow.**

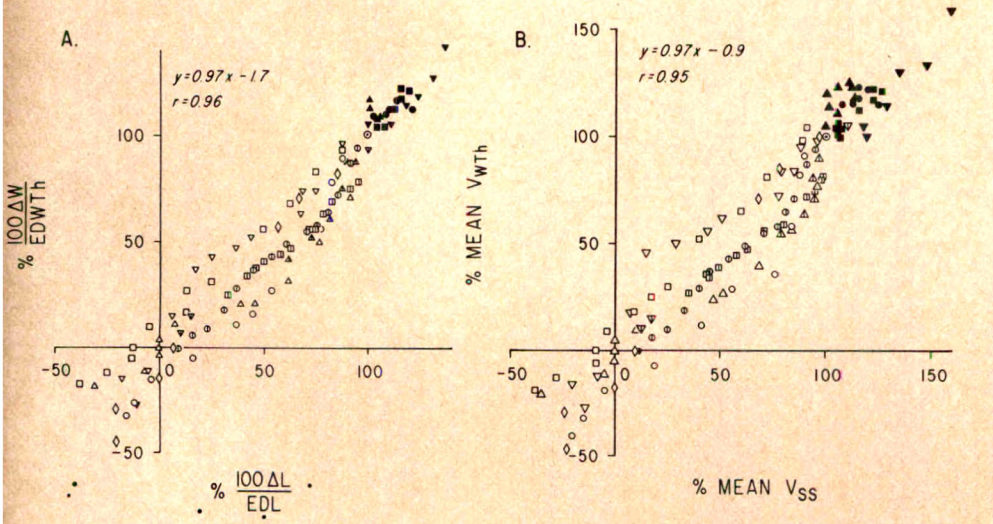


FIGURE 6. Changes in segment function and wall thickening during coronary occlusion. **A,** percent of control of normalized wall thickening and segmental shortening (abbreviations as in Figure 3C). **B,** percent of control of mean velocity of wall thickening (V_{WTh}) versus mean velocity of segmental shortening (mean V_{SS}). Each set of symbols indicates a series of beats in a given animal. Ischemic segments are shown by **open symbols** and control segments by **closed symbols.** Negative values occur during ischemia with systolic segment expansion and wall thinning.

then declined rapidly with progressive wall thickening associated with shortening of the internal chamber diameter. Immediately after aortic constriction, cross-sectional area remained constant in spite of significant changes in wall thickness and chamber diameter. Wall stress reached a maximal level later in ejection; this change was related to a delayed achievement of peak left ventricular pressure associated with reduced shortening of chamber diameter and diminished systolic wall thickening, peak wall stress being markedly increased. After sustained elevation of left ventricular pressure for an average of 18 days, there was an increase in wall thickness from an average left ventricular end-diastolic wall thickness of 10.2 to 11.3 mm (Table I); internal diameter returned to control level. This adaptation by hypertrophy has been shown to result in a decrease of peak wall stress to near normal.[26]

A linear relation was observed between wall thickness and internal diameter during systole after development of hypertrophy, as in the control state (Fig. 2). The slope of the loop is essentially unchanged from the control slope, but the intercept is higher. The parallel shift of the loop clearly indicates increased muscle mass. In hypertrophied hearts studied an average of 18 days after aortic constriction, internal chamber diameter decreased during ejection by 29 percent and the wall thickened by 28 percent of the end-diastolic value. The average of mean wall thickening velocity was 1.55 wall thicknesses/sec (range 0.84 to 2.19), similar to the average of the mean control shortening velocity of 1.61 diameters/sec (range 0.94 to 2.33) (Table I).

Discussion

The ultrasonic dimension gauges used in these experiments have proved useful in assessing segmental myocardial function,[27–29] and accordingly we have applied them to study instantaneous wall thickness changes. The stability of this gauge has also made it possible to apply it to the study of chronic animal preparations.[26] The approach provides for the continuous measurement of a thickness dimension without damaging the tissue between the crystals[26] and with minimal constraining or tethering effects on the subtended myocardium.[26–28] Using this method we have documented the time course of dynamic wall thickness changes during the cardiac cycle in normal conscious dogs and analyzed the relation of these changes to internal diameter and left ventricular pressure under several acutely and chronically changing conditions. Free wall thickness was examined in the mid regions of the left ventricle away from the bases of the papillary muscles. While it is possible that regions close to the atrioventricular ring and the apex might exhibit different dynamics, regions relatively close to the minor equator were selected for study because of accessibility and for purposes of comparison with the internal diameter in that region; despite some variability in the region of crystal placement, the wall thickening and segment dynamics were closely similar, and in other studies several simultaneous wall thickness measurements around the circumference also resembled one another closely. The internal diameter was chosen to resemble closely the minor axis used clinically in calculating velocity of circumferential fiber shortening (V_{CF}).[5]

Previous studies of wall thickness changes: Wall thickness changes observed during left ventricular isovolumic systole and ejection have varied widely. In most previous experimental studies, using devices connected mechanically across the wall, an increase in wall thickness of 6 to 10 percent during isovolumic systole was reported.[12–15] In one experiment in a single open chest dog, little or no change in wall thickness was found with use of an ultrasonic dimension gauge.[24] A decrease in wall thickness during the isovolumic period was found in anesthetized dogs with use of an electromagnetic coil transducer[16] and in conscious dogs with ultrasonic dimension transducers.[25] The papillary muscles have been shown to be the site of earliest activation,[33,34] and the mechanical sequence of contraction

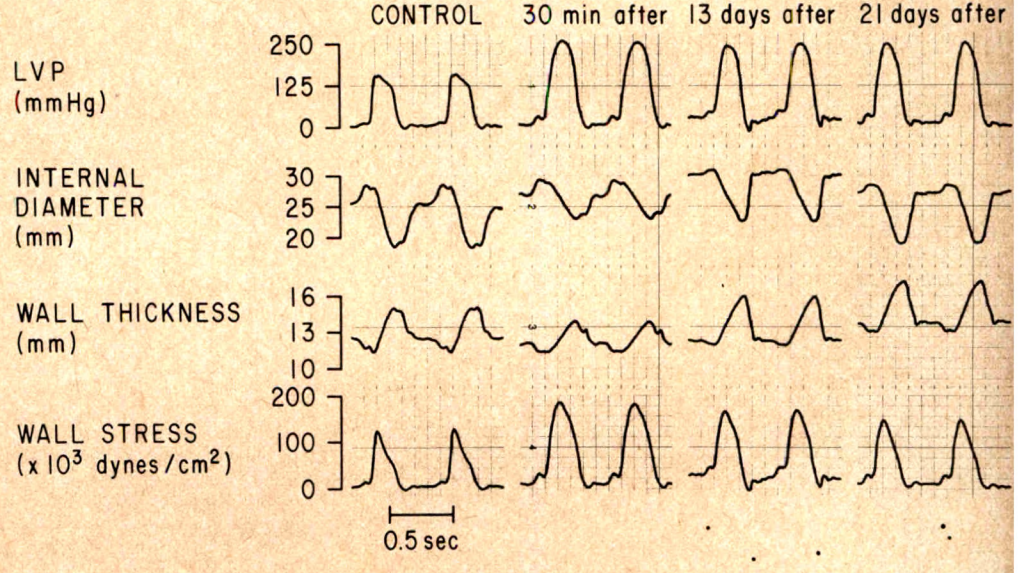


FIGURE 7. Effects of a sustained increase in afterload on left ventricular function in a conscious dog. Tracings were obtained during a control study and 30 minutes, 13 days and 21 days after aortic constriction. **From top to bottom:** left ventricular pressure (LVP), internal diameter, left ventricular force wall thickness and wall stress obtained by analog computation using the formula: WSt = (LVP × D)/4 WTh. Note the increase in wall thickness and reduction of wall stress over time, as chamber shortening returns to normal.

has been demonstrated to follow closely the depolarization pathway.[35–38] Therefore, proximity of the transducers to papillary muscles could account for occasional increases in wall thickness observed during isovolumic systole. In cineangiographic studies of patients, Eber et al.[6] noted that wall thickness remained relatively constant during the initial phase of ventricular systole, an observation also made in unanesthetized dogs by Lynch and Bove[8] using a high speed cineradiographic technique. Our observations provide direct support for these findings. There was a slight but significant decrease in internal diameter during isovolumic systole, a change also reported to occur in normal human hearts.[39]

During left ventricular ejection, wall thickness rapidly increased by 32 percent of its end-diastolic value at a control heart rate averaging 83 beats/min. This change is in reasonable agreement with the value of 28 percent obtained by Ross et al.[40] from direct measurement of hearts rapidly fixed at end-diastole or end-systole, and those of 33 percent reported by Gault et al.[5] using cineangiography and 34 percent reported by Belenkie et al.[20] using echocardiography in normal human subjects. In general, however, angiographic methods have usually substantially overestimated wall thickness because of infolding of trabeculae and the papillary muscles.[7,11,19]

There are few observations on ventricular wall thickness changes during atrial systole. Cothran et al.[13] reported an increase in left ventricular wall thickness during atrial systole in the horse, and suggested that this change might reflect increased myocardial blood volume resulting from impediment to the drainage of blood from the ventricular wall consequent to the increased right atrial pressure. This change was never observed in our studies; on the contrary, wall thickness always decreased during atrial contraction with a concomitant increase in left ventricular internal diameter, an observation also made by Guntheroth.[25] Cothran's observations presumably resulted from artifact produced by mercury-in-Silastic resistance gauges, which are subject to changes in cross-sectional area or length of the mercury column by compression or shearing forces. We have examined shear-related movements of the crystals using a single subendocardial crystal with a tripod, three crystal epicardial surface array[32]; small lateral movements do occur (±0.5 mm) resulting in an error in wall thickness measurement of less than 0.5 percent of end-diastolic wall thickness.

The accurate recording of instantaneous wall thickness changes as described in our study should allow more accurate descriptions of dynamic changes in wall stresses than previously available. Although it has generally been agreed that actual tensile stress is better approximated by thick-walled ellipsoidal models,[9,10] the simplified model used in our study illustrates the value of this approach for assessing relative dynamic changes in wall stress as a consequence of changes in wall thickness during various acute and chronic interventions, as well as for in vivo estimation of changes in ventricular mass.

Correlation of wall thickness change with ventricular function: Clinical implications: A linear relation obtained between wall thickness and internal diameter during left ventricular ejection, and end-diastolic diameters at different heart sizes induced by pacing or phenylephrine infusion also were linearly related to wall thickness in individual animals. The relation of wall thickness to internal diameter suggested that function and circumferential shortening characteristics of the wall could be inferred by measuring thickening of the wall alone. This proved to be the case, during both inotropic interventions and acute coronary occlusion.

When grouped data in all animals were considered, clear-cut linear relations could be shown between recognized measures of myocardial function (percent and velocity of reduction in chamber diameter or the dimension of a myocardial segment) and the extent and velocity of wall thickening during changes in afterload produced by phenylephrine and alterations in inotropic state induced by isoproterenol and propranolol (Fig. 4). These findings suggest that wall thickness changes alone measured with echocardiography at a single site may allow accurate assessment of overall left ventricular function in man, in the absence of regional dysfunction. Similar correlations were shown between regional segment length and wall thickness during the development of ischemia. Regional myocardial function after occlusion of the circumflex coronary artery was previously studied in unanesthetized dogs using ultrasonic crystals implanted subendocardially for the measurement of segment lengths.[27] Our present studies, in which wall thickness was measured simultaneously, showed reciprocal relations between end-diastolic and dynamic segment length and wall thickness, and linear correlations between the magnitude of changes in shortening extent and velocity and extent and velocity of wall thickening during partial and complete ischemia. The general form of the wall thickness changes reported herein closely resembles that of the changes described for the posterior wall of normal human subjects studied with echocardiography.[17–19] Our findings provide a firm experimental basis for using echocardiographic analysis of wall thickness in man[31] to evaluate the severity of regional dysfunction due to acute ischemia, as well as to assess myocardial and ventricular function in the absence of regional dysfunction.

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Coronary Steal: Its Role in Detrimental Effect of Isoproterenol After Acute Coronary Occlusion In Dogs

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Using epicardial electrograms others have established that infusion of isoproterenol increases myocardial injury after acute coronary occlusion. To define the contribution of alterations in collateral blood flow to this increased ischemia, isoproterenol was administered to 10 dogs. After pretreatment with practolol in doses that successfully block inotropic but not vascular effects of beta adrenergic stimulants, intracoronary isoproterenol continued to enhance the magnitude of S-T segment elevation in ischemic areas. Thus, vasodilation induced by isoproterenol appears to divert flow from the ischemic area. To test this hypothesis, intracoronary adenosine was given to cause coronary vasodilation without enhancing inotropy. S-T segment elevation at ischemic and adjacent sites was significantly increased. Neither agent had systemic effects, but each increased coronary blood flow while concomitantly decreasing collateral flow as evidenced by a reduction in retrograde coronary flow and peripheral coronary pressure. In addition, adenosine significantly diminished the rate of xenon-133 clearance from the ischemic myocardium. Thus, isoproterenol, in addition to its positive inotropic effect, increases myocardial injury by its vascular action. Collateral blood flow to acutely ischemic myocardium is diminished by the production of a coronary steal. Intravenously administered isoproterenol additionally diminishes collateral flow by decreasing coronary perfusion pressure. It is postulated that any agent that causes either a primary or secondary coronary vasodilation may cause a coronary steal and subsequently enhance myocardial injury.

The feasibility of limiting the extent of myocardial ischemia by either mechanical or pharmacologic means has been extensively examined in an animal model.[1–14] This approach may have important clinical applications if therapeutic measures can be developed to limit successfully the extent of myocardial necrosis after acute coronary occlusion. The rational introduction of experimental techniques into a coronary care unit requires awareness of the mechanism by which agents either exacerbate or ameliorate myocardial ischemia. Although alteration of myocardial metabolism is widely recognized as one such mechanism,[2] surprisingly little attention has been focused on the effect of changes in coronary collateral blood flow. A coronary vasodilator might be one's first choice as an agent for enhancing myocardial survival. However, agents that dilate arterioles in normal areas may initiate a "coronary steal" in the ischemic area and have an associated deleterious effect on indexes of ischemia.

Isoproterenol is both a potent positive inotropic agent and a coronary vasodilator, and both properties may be deleterious to ischemic muscle. Accordingly, in these experiments we studied the changes in collateral flow and subsequent ischemic injury induced by isoproterenol. This

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agent, which is capable of dilating the coronary vasculature directly, as well as indirectly because of the enhanced myocardial metabolism, diminished collateral flow and aggravated myocardial ischemia. These studies emphasize that agents may affect infarct size by modifying either collateral blood flow or myocardial metabolism.

Methods

Experiments were performed in 22 mongrel dogs anesthetized with sodium pentobarbital (27.5 mg/kg body weight). Additional amounts were administered as required to maintain prolonged anesthesia. A polyvinyl catheter was introduced into the thoracic aorta through a femoral artery for measurement of systemic pressure with a Statham transducer. After endotracheal intubation and mechanical ventilation with an intermittent positive pressure respirator using 100 percent oxygen, a left thoracotomy was performed. Anticoagulation was produced by injection of 20,000 units of heparin and maintained by injection of 10,000 units every 1 to 2 hours.

Experimental preparation: In 10 animals the main left coronary artery was cannulated with a modified Gregg cannula introduced into the left subclavian artery and securely tied in place just proximal to the main left coronary bifurcation (Fig. 1). The resistance of the perfusion tubing from the location of the proximal coronary pressure gauge to the tip of the Gregg cannula used in these animals was determined with blood and found to be 1.4 mm Hg-min/100 ml over the range of flow values encountered. The coronary vascular bed was perfused with blood from a femoral artery. The perfusion tubing also contained an extracorporeal flow probe attached to a Biotronex 410 electromagnetic flow meter, a side arm for measurement of coronary perfusion pressure with a Statham transducer, and a site for intracoronary drug injection. This preparation showed marked autoregulation of coronary blood flow so that steady state coronary resistance decreased when perfusion pressure was lowered from the control level.[15] Maintenance of constant coronary pressure was achieved by perfusion from a reservoir (Fig. 1). The level of perfusion pressure was determined by the height of the reservoir. Either the distal left anterior descending coronary artery or the major diagonal branch was isolated and a suture passed underneath it. Myocardial contractile force was measured in normal areas with an isometric strain gauge arch (manufacturer, John Warren, P.O. Box 412, Charlestown, S. C. 29402) sewn to the epicardium and oriented parallel to the superficial fibers. A polyvinyl catheter was introduced into the left ventricular cavity through the left atrial appendage to measure end-diastolic pressure. The first derivative of left ventricular pressure (dP/dt) was obtained by electronically differentiating the left ventricular pressure. An epicardial electrogram was recorded with an exploring electrode consisting of a saline-impregnated cotton wick in a 0.4 cm diameter metal cylinder. A Wilson central terminal formed from three limb leads was used as the negative lead. The gain of the signal was adjusted so that 1 mv was equivalent to 1 mm on the recording paper. All signals were recorded directly on a multichannel oscillograph.

Freshly prepared saline solutions of isoproterenol and adenosine were administered to these animals. A continuous intracoronary infusion of adenosine (Sigma Chemical), 0.58 mg/min, was delivered with the aid of a Harvard Apparatus constant infusion pump. Isoproterenol was injected directly into the perfusion tubing at a rate of 0.29 μg/min. The infusion rate of isoproterenol was increased 10-fold in animals receiving the drug intravenously.

Epicardial S-T mapping: Experiments in 11 dogs demonstrated the reproducibility of epicardial mapping in experimental animals. Ligation of the left anterior descending artery produced maximal S-T segment elevation at distal sites within 7 minutes. Thereafter there were no consistent changes up to 25 minutes. Ventricular arrhythmias were conspicuously absent during the 25 minute observation period in most of the preparations, and the hemodynamic state was stable. Release of the snare promptly returned S-T segments to control levels. Reocclusion after a 30 minute equilibration period produced S-T segment elevations similar to those initially seen. These results confirm data from earlier reports.[2,3,16] The use-

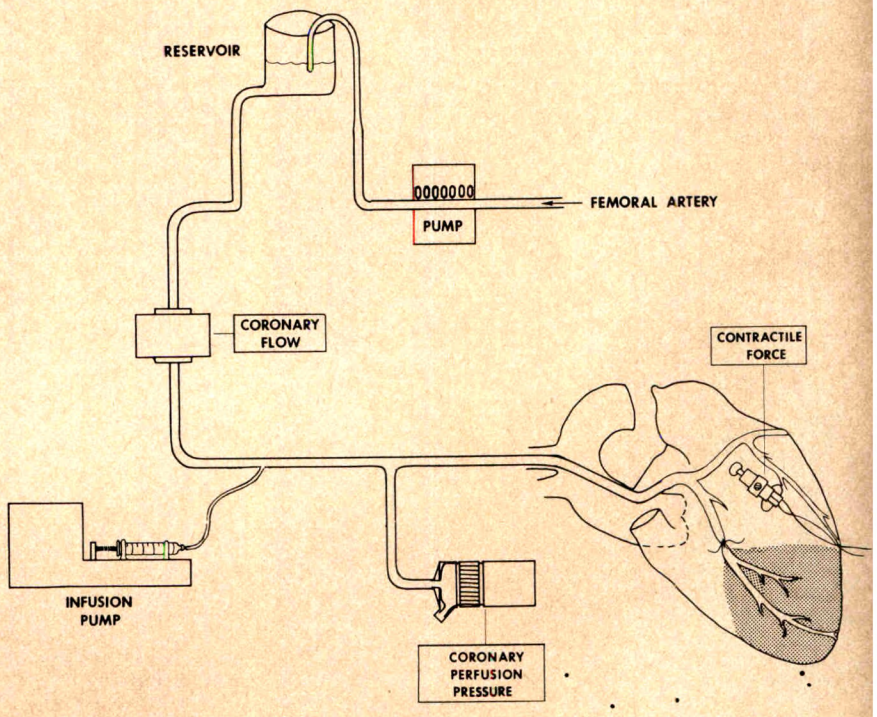


FIGURE 1. Experimental preparation. The reservoir was used to maintain a constant coronary perfusion pressure. The **stippled area** represents ischemic myocardium distal to the ligature around the coronary artery.

fulness of epicardial mapping in the documentation of regional myocardial ischemia has been demonstrated by others.[2,5–7,13,17–19]

Protocol: In these experimental animals the isolated coronary arterial branch could be reversibly occluded with a snare. Coronary perfusion from the constant pressure reservoir was commenced, and a control electrogram was recorded from 12 to 14 epicardial sites. Approximately six of these sites were distal to the ligature and in the potentially ischemic zone. Coronary perfusion pressure, coronary blood flow, left ventricular pressure, left ventricular dP/dt, strain gauge arch deflection and systemic pressure were recorded during brief periods of apnea. The coronary vessel was then occluded. After 7 to 8 minutes all variables were recorded again, and a second set of epicardial electrograms was recorded. While the coronary occlusion was maintained, intracoronary infusion of either isoproterenol or the vasodilator adenosine was administered to 10 animals. Recording of all measurements including epicardial electrograms was performed at least 7 minutes after the start of the infusion. The infusion was then discontinued, the snare released, and the animal allowed to recover for at least 30 minutes. The sequence was then repeated with intracoronary infusion of the second vasodilator. After a second recovery period of approximately 30 minutes, the 8 animals with successful isoproterenol infusions were treated with intravenously administered practolol, 1.25 mg/kg. After confirmation of the adequacy of blockade of the positive inotropic effects of an intracoronary bolus injection of 0.2 μg of isoproterenol, the previous sequence was again repeated during continuous infusion of isoproterenol.

Four animals were prepared in a similar fashion without cannulation of the main left coronary artery. In these animals the effect of intravenous infusion of isoproterenol on systemic pressure, left ventricular pressure, left ventricular dP/dt, strain gauge arch recording and the epicardial electrogram before and after beta adrenergic blockade with practolol was demonstrated.

After completion of these studies in 6 of the 10 animals with an indwelling Gregg cannula and in 3 of the 4 animals without a main left coronary arterial cannula, a catheter was introduced into the coronary branch at the site of prior isolation. Retrograde blood flow and mean distal coronary pressure were recorded under control conditions in these animals. The effects of intracoronary administration of adenosine and isoproterenol after treatment with practolol were noted in the animals with Gregg cannulas in place, whereas only intravenous infusion of isoproterenol was used in the three animals with an intact coronary circulation.

Xenon-133 clearance studies: Xenon-133 clearance[20] was used as a second index of collateral blood flow during intracoronary administration of adenosine in eight dogs. In these animals a Gregg cannula was inserted into the main left coronary artery and a branch of the left anterior descending artery was isolated as before. The latter branch was then ligated proximally and the distal end cannulated. Blood flow was then restored to this branch by diverting blood to it from the main perfusion tubing. Gamma emission from xenon-133 was detected with a collimated sodium iodide crystal that was connected to a linear rate meter. During cessation of flow to this branch, 0.01 to 0.02 ml of a solution of xenon in saline solution was injected into its perfusion tubing and gently flushed into the distal vascular bed with 3 to 5 ml of blood or saline solution. A xenon-133 washout curve was continuously recorded for approximately 2 minutes during the control state, for two minutes during a constant intracoronary infusion of adenosine, and for 2 to 3 minutes after discontinuation of the infusion. At the end of this period the occlusion was released and blood flow restored to the ischemic myocardium. Intracoronary administration of adenosine elicits coronary dilation and increased coronary flow within 10 to 15 seconds of the start of infusion, and its vascular effects are terminated within 20 seconds of the end of administration. The rapid onset and decay of effect permit the recording of the sequence described during one xenon clearance. Sixteen xenon-133 clearances were recorded in this manner.

Despite the use of a constant pressure perfusion apparatus, the increase in flow induced by intracoronary infusion of adenosine caused a small decrease in coronary perfusion pressure. To evaluate the effect of a decrease in coronary pressure, epicardial S-T segments, retrograde flow and xenon-133 clearance were measured after lowering of the reservoir.

TABLE I

Effect of Coronary Arterial Occlusion and Vasodilator Drugs on Hemodynamic Variables and Epicardial Electrograms (mean ± standard error of the mean)

Dogs (no.)	First Intervention	Epicardial Electrogram ΣS-T (mv)	Epicardial Electrogram N-ST	Second Intervention	Epicardial Electrogram ΣS-T (mv)	Epicardial Electrogram N-ST	Changes Induced by Addition of Intervention 2 to Intervention 1: Δ Coronary Blood Flow (ml/min)	Δ Coronary Pressure (mm Hg)	Δ Strain Gauge Arch Deflection (%)	Δ LV dP/dt (maximum) (%)	Δ Mean Blood Pressure (mm Hg)	Δ Heart Rate (beats/min)
10	LAD occl	13.2 ±2.9	4.1 ±0.7	IC A	28.1 ±4.8†	5.7 ±0.7†	85.0 ±12.3	−6.6 ±1.0	−4.7 ±2.5	−5.7 ±1.4	−4.2 ±2.3	2.9 ±5.7
8	LAD occl	16.0 ±6.8	3.2 ±0.7	IC Iso	34.6 ±7.9†	5.9 ±0.8†	22.2 ±3.6	−1.8 ±0.8	95.8 ±11.7	52.9 ±5.6	6.1 ±2.8	4.4 ±3.3
7*	Practolol + LAD occl	10.1 ±3.0¶	4.4 ±0.9¶	IC Iso	17.4 ±3.5†§	5.7 ±0.8†¶	18.3 ±4.5¶	−0.9 ±0.9¶	13.3 ±2.5§	7.0 ±1.8§	4.0 ±3.1¶	−0.1 ±1.2
4	LAD occl	8.9 ±1.3	3.2 ±0.2	IV Iso	31.9 ±2.4†	6.5 ±0.6†	—	—	67.0 ±5.5	54.7 ±9.3	−13.8 ±3.4	28.2 ±8.2
4	Practolol + LAD occl	9.1 ±1.7¶	4.8 ±0.6¶	IV Iso	19.3 ±1.6†§	6.3 ±0.9‡¶	—	—	6.0 ±3.1§	9.3 ±2.4§	−12.5 ±3.4¶	10.8 ±3.6¶

*Practolol blocked the coronary vascular responses in one animal, and the results obtained in this experiment are not included in the calculations.

†‡§¶ Statistical analysis of changes in epicardial electrograms induced by addition of intervention 2 († $P < 0.05$; ‡ not significant); statistical analysis of effect of practolol on changes induced by interventions 1 and 2 in hemodynamic variables and epicardial electrograms: § $P < 0.05$; ¶ not significant.

A = adenosine; Δ = change; IC = intracoronary; Iso = isoproterenol; IV = intravenous; LAD = left anterior descending coronary artery; LV = left ventricular; N-ST = number of epicardial sites with S-T segment elevation greater than 1.5 mv; occl = occlusion; ΣS-T = sum of S-T segment elevations recorded from ischemic epicardial sites.

Calculations: Analysis of all epicardial electrograms was performed in a manner similar to that of Maroko et al.[2] At each recording site the S-T segment deviation present before coronary occlusion was subtracted from the amount present afterwards to determine the S-T segment change elicited by ischemia. S-T elevation greater than 1.5 mv was considered significant. Significant S-T depression was sometimes observed in sites in the marginal area between normal and ischemic myocardium. These sites were omitted from the final calculations. The summation of changes in S-T elevation (Σ S-T) has been suggested to represent the degree of myocardial ischemia, and the number of sites with significant S-T elevation (N-ST) the extent of ischemia.[2]

All xenon-133 washout curves were replotted on semilogarithmic paper and the best straight line fitted by eye to the points. The half-time decay ($t_{1/2}$) was determined from the slope, and flows were calculated according to the equation[21]: flow = $K/t_{1/2}$. Any sequence of xenon-133 washouts in which the flow after discontinuation of infusion of adenosine did not return toward control level was not used in the calculations. Therefore, 10 sequences in six animals were analyzed.

All results are expressed as means ± standard error of the mean. Student's test for independent observations was used to determine the significance of differences.[22]

Results

Hemodynamic measurements in the control animals during 25 minute occlusions of the distal left anterior descending coronary artery or major diagonal branch were quite stable. For the animals used in these experiments control systolic left ventricular pressure was 122.3 ± 3.1 mm Hg, left ventricular end-diastolic pressure 3.0 ± 0.8 mm Hg, mean coronary flow 99.4 ± 11.2 ml/min and heart rate 171.8 ± 8.0 beats/min.

Effects of isoproterenol: The effects of isoproterenol and adenosine on epicardial electrograms and hemodynamics are tabulated in Table I. Both intracoronary and intravenous isoproterenol infusions significantly increased the degree and extent of ischemia ($P < 0.025$) (Fig. 2). During intracoronary infusion, coronary blood flow increased by an average of 22.2 ± 3.6 ml/min. During intravenous infusion of isoproterenol, mean systolic pressure decreased by 14.3 ± 4.7 mm Hg. Practolol significantly blocked the inotropic effect of isoproterenol. Despite this blockade, intracoronary administration of isoproterenol continued to increase significantly the ischemic injury, although the increments were less than those seen before the administration of practolol (average Σ S-T increased from 16.0 to 34.6 mv before administration of practolol and from 10.1 to 17.4 mv after beta blockade) (Fig. 3). Intravenous administration of isoproterenol elicited similar changes (average Σ S-T increased from 8.9 to 31.9 mv before practolol and from 9.1 to 19.3 mv after beta blockade) (Table I). Practolol did not alter the vascular effects of this catecholamine, as indicated by similar reductions in pressure. In seven of eight dogs treated with practolol, intracoronary infusion of isoproterenol increased coronary flow by an average of 18.3 ± 4.5 ml/min; only in one animal was there no increase in coronary blood flow. In this animal differential blockade was not successful, and there was no further elevation of S-T segments during infusion of isoproterenol. These data were not included in the statistical analysis.

Effects of adenosine: Because practolol blockade of the inotropic action of isoproterenol was not complete, the effect of adenosine, a vasodilator without inotropic properties, on the same indexes of ischemia was investigated. In the presence of an occluded left anterior descending artery, adenosine significantly increased

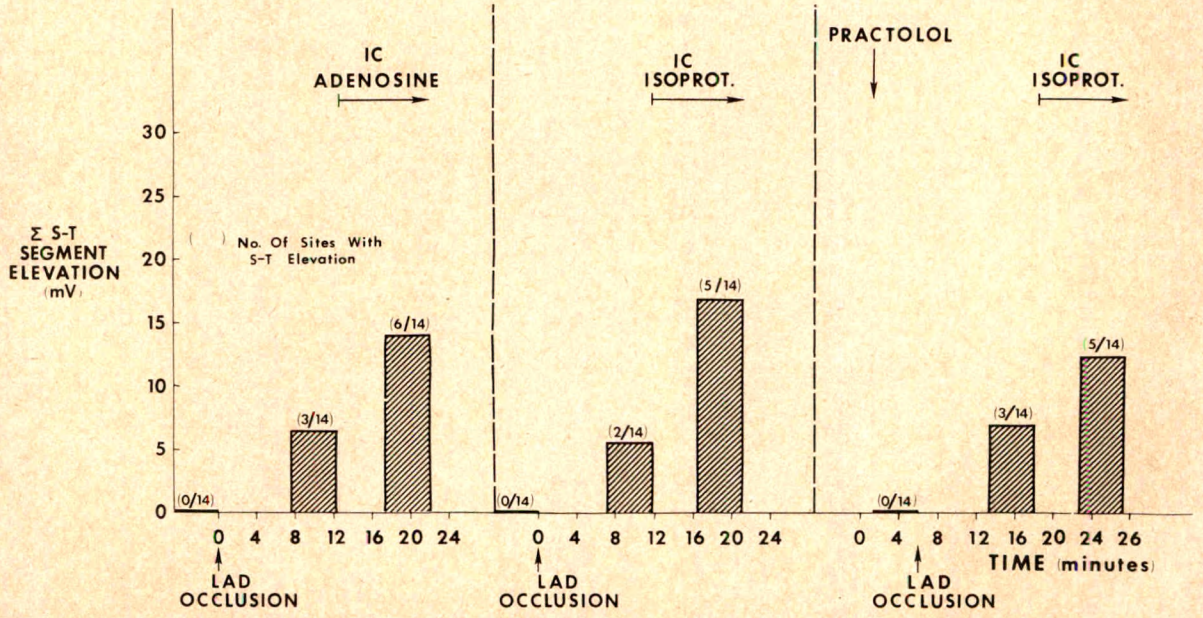


FIGURE 2. Effects of vasodilators on myocardial ischemia as indicated by the summation of S-T segment elevation (Σ S-T) and the number of sites in the ischemic area in one representative experiment. The intracoronary (IC) administration of adenosine **(left panel)** after occlusion of the left anterior descending coronary artery (LAD) increased myocardial ischemia. The intracoronary infusion of isoproterenol (ISOPROT.) produced significant myocardial injury **(center panel).** After selective blockade of the inotropic properties was produced with practolol, intracoronary administration of isoproterenol **(right panel)** continued to increase myocardial injury, documenting the deleterious effect of coronary vasodilation in this model.

both the degree (Σ S-T) (P <0.001) and extent (N-ST) (P <0.025) of myocardial ischemia (Fig. 4). During the period of drug infusion, coronary blood flow increased by 85.0 ± 12.3 ml/min (range 34 to 167 ml/min). However, there was no evidence of enhanced inotropy as documented by recordings of left ventricular dP/dt and strain gauge deflection.

Retrograde flow and peripheral coronary pressure (Fig. 5, Table II): Isoproterenol decreased retrograde flow by 20.1 ± 4.9 percent when injected directly into the coronary circulation and by 24.5 ± 1.9 percent when injected intravenously. Peripheral coronary pressure decreased by 18.7 ± 5.4 percent and 23.0 ± 3.2 percent, respectively. Retrograde flow was diminished 37.5 ± 3.5 percent by intracoronary administration of adenosine, and peripheral coronary pressure decreased by an average of 8.0 mm Hg.

Xenon-133 clearance: Adenosine significantly affected the clearance of xenon-133 from the ischemic area (Fig. 6). Collateral blood flow before drug infusion averaged 16.1 ± 3.1 ml/min per 100 g. Adenosine decreased the flow by 59.5 ± 7.3 percent (Table II). The intracoronary infusion of adenosine increased coronary blood flow concomitantly with a visible change in slope of the xenon-133 clearance curve. With termination of the adenosine infusion coronary flow returned to its control level, and the clearance returned to within 10 percent of the pre-adenosine level. The six discarded

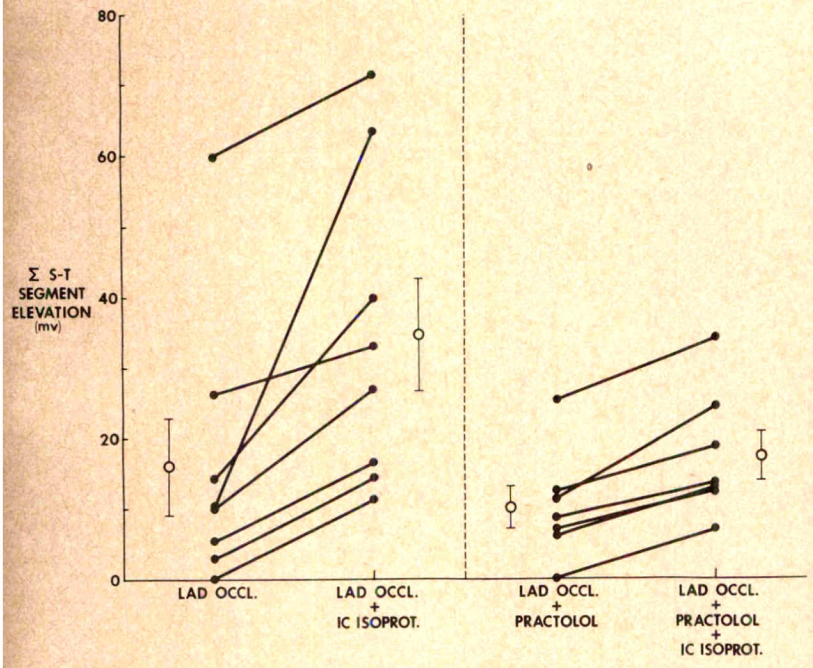


FIGURE 3. Data for all dogs with occlusion of the left anterior descending coronary artery (LAD OCCL.) studied during intracoronary (IC) infusion of isoproterenol (ISOPROT.) before **(left panel)** and after **(right panel)** beta blockade with practolol. The **heavy lines** connect data points in single animals. The **open circles** represent the means, and the length of the **vertical bars** denotes 2 standard errors of the mean. The difference between the means in the two panels is statistically significant.

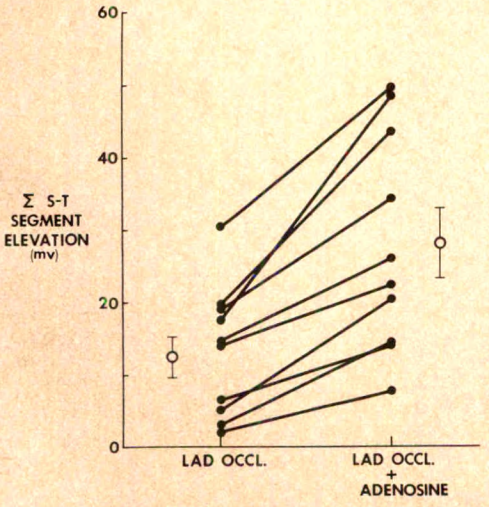


FIGURE 4. Data for all dogs studied during intracoronary infusion of adenosine. The **heavy lines** connect data points in single animals. The **open circles** represent the means, and the length of the **vertical bars** denotes 2 standard errors of the mean. The difference between the means is statistically significant. Abbreviations as in Figure 3.

TABLE II

Effect of Vasodilator Drugs on Collateral Blood Flow (mean ± standard error of the mean)

	Control Collateral Indexes				Drug-Induced Change (%)		
Dogs (no.)	Retrograde Flow (ml/min)	Xenon-133 Washout (ml/min per 100 g)	PCP (mm Hg)	Intervention	Retrograde Flow	Xenon-133 Washout	PCP
4	1.9 ±0.3	...	39.0 ±4.5	IC Iso	−20.1 ±4.9*	...	−18.7 ±5.4*
3	1.5 ±0.2	...	27.7 ±3.9	IV Iso	−24.5 ±1.9*	...	−23.0 ±3.2*
6	3.2 ±1.0	...	37.8 ±2.5	IC A	−37.5 ±3.5*†	...	−22.8 ±3.5*†
6	...	16.1 ±3.1	...	IC A	...	−59.5 ± 7.3*†	...

*All drug-induced changes were statistically significant (P <0.05).

†Because of the small decrease in coronary perfusion pressure induced by intracoronary adenosine, these values slightly overestimate the effect of the agent itself. See text.

PCP = peripheral coronary pressure; other abbreviations as in Table I.

clearance experiments also demonstrated marked diminution of isotope washout during adenosine infusion. However, because the clearance did not increase to control levels after discontinuation of drug administration, reliability of the clearance measurements was questioned. Therefore, to avoid bias, these experiments were not included in the calculations.

Effects of decreased perfusion pressure: Despite the use of a coronary perfusion reservoir, the large increment in coronary flow of 85.0 ± 12.3 ml/min induced by adenosine infusion resulted in a decrease in pressure in the perfusion tubing averaging 6.6 mm Hg (Table I). The perfusion reservoir was mechanically lowered on five occasions in three animals to examine the effect of decreased perfusion pressure. For an average decrease in pressure of 15.4 ± 3.8 mm Hg, the average change of ΣS-T elevation of 5.1 ± 3.5 mv was noted over 14 sites. This is consistent with calculations made using the published regression equation relating ΣS-T to changes in mean perfusion pressure.[2] The difference between the effects on the degree of ischemia elicited by adenosine and simple reduction of perfusion pressure remains highly significant ($P < 0.001$). Comparable decrements in coronary perfusion pressure caused retrograde flow to be diminished by 15.2 ± 6.4 percent, and xenon-133 clearance by 8.6 ± 5.6 percent. These adjustments do not substantially alter the quantitative significance of the effects of adenosine on the measurements of collateral flow.

Discussion

Our study demonstrated that isoproterenol, as well as the potent coronary vasodilator adenosine, may further diminish the blood flow to ischemic myocardium and subsequently increase the magnitude of observed ischemia. Apparently vasodilation in normal areas induces a reduction of blood flow in ischemic myocardium even though measured coronary perfusion pressure is unchanged. This phenomenon has been termed "coronary steal." [23] Other manipulations including infusion of mannitol,[8] counterpulsation[11,12,24] and changes in coronary perfusion pressure[2,9,14,25,26] have been docu-

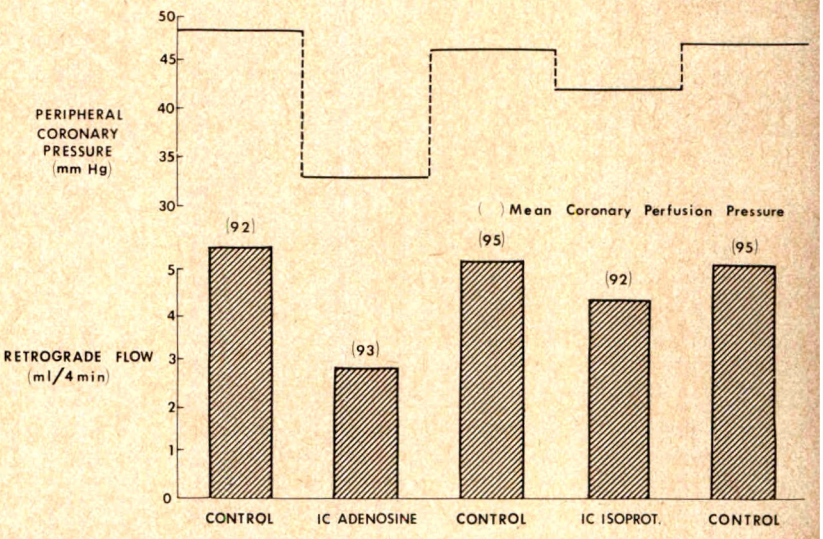


FIGURE 5. Effects of intracoronary administration of adenosine and isoproterenol on retrograde flow and peripheral coronary pressure in a representative animal. Adenosine and isoproterenol each decreased these two indexes of collateral flow in proportion to the degree of induced coronary vasodilation. Abbreviations as in Figure 3.

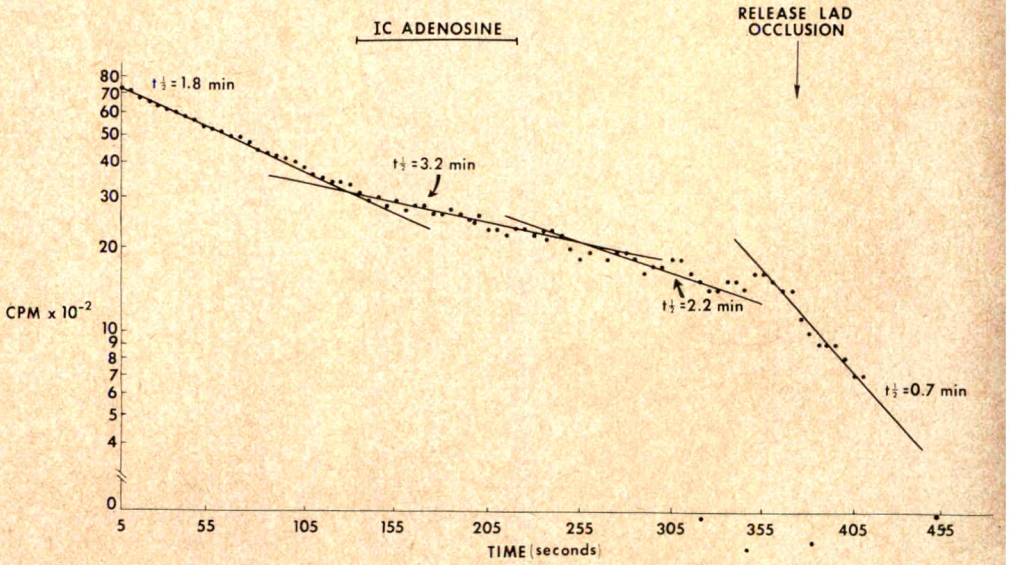


FIGURE 6. Effect of intracoronary administration of adenosine on xenon-133 clearance from an ischemic myocardial area in a representative animal. Xenon-133 was injected into the distal portion of the occluded vessel, and the clearance was measured before, during, and after administration of adenosine, and after release of occlusion of the left anterior descending coronary artery. The count rate recorded from the precordial area is presented semilogarithmically. The half-time ($t_{1/2}$) for each part of the experiment is indicated. CPM = counts per minute; other abbreviations as in Figure 3.

mented to affect directly both collateral blood flow and ischemia. Ischemia may also be directly affected by agents altering myocardial metabolism. However, agents that increase metabolic demands will also elicit secondary increases in flow to normal myocardium and hence have the potential to initiate a coronary steal. Thus, in attempting to define the mechanism by which agents or interventions affect myocardial ischemia, we suggest that the dual actions on collateral flow and myocardial metabolism should be considered.

Inotropic versus vasodilating effects of isoproterenol: Maroko et al.[2] have previously demonstrated that intravenous administration of isoproterenol increases the extent as well as the intensity of myocardial ischemia. We are able to confirm this observation, and extend it to the use of intracoronary infusion of isoproterenol. This drug has a significant positive inotropic effect and increases both maximal left ventricular dP/dt and the magnitude of deflection of the strain gauge arch (Table I). In order to separate the metabolic and vascular effects of this drug, we administered practolol to the experimental animals. Mark et al.[27] demonstrated that small doses of this agent produce a selective blockade of isoproterenol's inotropic effect while preserving the vasodilatory activity mediated by beta adrenergic receptors in the coronary and peripheral vasculature. Table I indicates that the dose of practolol used had little effect on the ability of isoproterenol to increase coronary blood flow when administered by the intracoronary route or to decrease systemic pressure when given intravenously. However, the inotropic effect after beta blockade was approximately one-eighth of that before administration of practolol. Under these conditions isoproterenol continued to increase the intensity and area of myocardial ischemia (Fig. 3), although the response was reduced. The increment in the sum of S-T elevation was 40 percent as great as that before administration of practolol.

Coronary steal mechanism: The vasodilatory property of isoproterenol is the probable cause of these observations. This agent dilates the coronary vasculature in the normally perfused myocardial areas while having no effect on the already dilated arterioles in the ischemic region distal to the arterial occlusion. Blood flow to the normal area increases and, because of the relatively fixed resistance of the large proximal coronary arterial segments, the perfusion pressure at the origin of the collateral vessels decreases with resultant reduction of collateral blood flow. Blood vessels supplying the ischemic area cannot further dilate to compensate for this fall in pressure. Thus ischemia is increased.

This mechanism, a coronary steal, has been demonstrated with other vasodilators in experimental animals. Although Kattus and Gregg[25] were unable to explain the decrease in retrograde flow following administration of nitroglycerin to dogs, their observation perhaps represents the earliest reported example of coronary steal. Khouri and Iza[28] have documented a diminution in collateral flow to ischemic regions after intracoronary administration of nitroglycerin. After acute coronary occlusion, carbochromen elicits marked decrements in collateral flow in some dogs while significantly augmenting flow in normal areas, although the observed decrease in collateral flow was not statistically significant for the entire experimental group.[29] Collateral flow is also diminished while total coronary flow is increased after administration of dipyridamole in dogs with acute[30] and chronic[31,32] coronary obstruction. Thus adverse effects on collateral blood flow are not unique to the dilating drugs used in our study.

Coronary steal may also be responsible for redistribution of blood flow across the myocardial wall. Recently, Forman et al.[33] demonstrated a diminished flow to ischemic myocardium and appearance of subendocardial ischemia after administration of nitroglycerin to animals with critical levels of coronary obstruction. Several years earlier, based on analysis of a model of the coronary circulation, Winbury et al.[34] had postulated a flow redistribution favoring the epicardium after administration of either dipyridamole or chromonar. A transmyocardial flow redistribution has been documented after infusion of lidoflazine[35] and dipyridamole,[36] as well as after the combination of carbochromen treatment and pacing-induced tachycardia[37] in dogs with chronic coronary arterial occlusion.

To test more rigorously the hypothesis that a coronary dilator may be injurious to the heart, we infused adenosine, a powerful vasodilator without any direct inotropic or metabolic effects. This drug clearly aggravated the ischemia distal to the occlusion of a coronary artery. Because this agent is known to have principally vascular effects, it seems certain that the cause of the increased ischemia is decreased collateral flow initiated by a coronary steal.

Role of reduced coronary perfusion pressure: An attempt to quantitate the decrement in collateral flow induced by both adenosine and isoproterenol was made by measuring the amount of backbleeding from the segment of the coronary artery distal to the occlusion. Adenosine induced a 37.5 ± 3.5 percent decrease in this index of collateral flow. In our experiments the small uncontrolled pressure drop induced by intracoronary adenosine would result in only a 9 percent decrease in retrograde flow according to the data of Brown et al.,[26] whereas our more limited direct measurements suggest a decrease of approximately 15 percent. Therefore, this would indicate there was a net decrease of at least 23 percent caused by the direct action of this drug on the coronary vasculature. Isoproterenol, when infused into the coronary artery of dogs previously treated with practolol, had little effect on coronary perfusion pressure and decreased the amount of retrograde flow by 20 percent. Intravenously administered isoproterenol would be expected to affect collateral flow by two mechanisms: a "coronary steal" similar to that initiated by intracoronary drug infusion, and a decrease in aortic diastolic pressure secondary to the agent's peripheral vasodilation. Previous studies using intravenously administered isoproterenol[2,14] have documented a reduction in perfusion pressure but have failed to consider the effect of this change in perfusion pressure on collateral flow and developing ischemia. In our present study, isoproterenol decreased mean systemic pressure by 14.3 mm Hg and therefore would be expected to de-

crease retrograde flow by approximately 16 percent.[26] We measured a reduction of 25 percent and suggest that the additional decrement of 9 percent was caused by the drug's direct effect on the coronary vasculature. The decrease in peripheral coronary pressure after administration of either isoproterenol or adenosine corresponds to the changes in retrograde flow (Table II).

Despite the obvious changes in retrograde flow induced by both isoproterenol and adenosine, it has been suggested that this measurement does not represent total collateral flow.[38] In an attempt to assess more directly the effect of coronary vasodilation on total collateral flow, we also measured the rate of xenon-133 clearance from the myocardium distal to the occlusion. Adenosine prolonged clearance rates 59.9 percent, thus indicating that this drug significantly decreased collateral blood flow. Because of the relatively brief duration of the three phases of each xenon-133 experiment, a single compartment analysis was necessary and we were unable to detect heterogeneity of collateral flow.[20,39] However, the change in clearance during administration of adenosine cannot merely be attributed to the appearance of a slow flow component because clearance in each reported case returned toward control rates when infusion of adenosine was discontinued.

The changes in collateral flow reported here are associated with large S-T segment shifts. Epicardial electrograms are apparently very sensitive to small changes in flow to the ischemic area although the precise nature of the relation between flow and S-T segment elevation is unknown.

Role of vasodilating drugs in myocardial ischemia: This study demonstrates coronary steal induced by both isoproterenol and adenosine after complete coronary occlusion. To initiate a steal there must be two parallel vascular pathways with a proximal common segment. In this study, one pathway was able to undergo dilatation in response to administered agents (the normal left circumflex system), while the other was nearly maximally dilated (the ischemic left anterior descending system). The proximal common segment either did not respond to the dilating stimulus or responded to a smaller degree than the distal vascular bed. Our experiments show that coronary steal can be induced when the large coronary vessels are normal. In patients with coronary atherosclerosis, proximal coronary lesions would further diminish distal coronary pressure after the administration of vasodilating agents and would be expected to increase the magnitude and significance of the coronary steal phenomenon. On the other hand, some coronary vasodilators could increase collateral blood flow and diminish myocardial ischemia if their effects were limited to the proximal common segment, to vessels in the ischemic region or to the collateral channels.[32]

The increase of S-T elevation induced by isoproterenol was significantly less after blockade with practolol ($P < 0.025$), thus suggesting that the drug's inotropic property accounts for part of the detrimental effect. To document the direct metabolic effect of isoproterenol on ischemic myocardium, in preliminary experiments in four dogs the drug was continuously infused into the coronary circulation while the vasculature was maximally dilated by adenosine. Since isoproterenol could effect no additional vasodilation, any alteration in ischemic injury would be secondary to this drug's positive inotropic action. Under these experimental conditions ΣS-T was increased, suggesting that alteration of the myocardial metabolic state is indeed an independent determinant of this index.

Although isoproterenol increases the myocardial oxygen consumption of normal myocardium,[40] its effect on ischemic muscle is not clear. Oxygen extraction in the ischemic area would be expected to be maximal. Therefore, a diminution of collateral blood flow during infusion of isoproterenol would decrease oxygen availability and might subsequently decrease oxygen consumption. Despite a net decrease in oxygen consumption of the ischemic muscle, the diminished availability of oxygen coupled with the enhanced metabolic state initiated by isoproterenol would further disturb the balance between oxygen supply and demand and thus aggravate the degree of ischemia.

Clinical implications: Extrapolation of these observations to the clinical situation must be done with caution since the described experiments were performed in open chest mongrel dogs. The results of administration of isoproterenol and other vasodilators will be influenced by the prevailing venous and arterial vasomotor tone. Furthermore systemic vasodilators that decrease preload or afterload, or both, will act to diminish myocardial wall tension and therefore oxygen consumption. Reduction of preload may also directly augment collateral flow.[41] Vasodilators have multiple physiologic properties, and complex interactions will determine their ultimate effect. Thus our experimental model greatly simplifies the actual clinical setting but serves to emphasize one potential malignant effect of vasodilators.

The role of changing collateral blood flow should be considered for any agent that alters infarct size after acute occlusion of a coronary artery. As demonstrated in this study, isoproterenol aggravates ischemia distal to a coronary occlusion by decreasing collateral flow. As demonstrated by our preliminary experiments, and as suggested by others,[2] isoproterenol also increased ischemia by metabolic stimulation. A second intervention, counterpulsation, also affects both collateral flow[24] and cardiac metabolism[42,43]; increased flow and decreased myocardial work and oxygen consumption result in amelioration of myocardial injury. Any pharmacologic or mechanical agent altering myocardial metabolism will secondarily induce a change in coronary blood flow by an autoregulatory process and subsequently affect the magnitude of coronary steal and therefore collateral flow. It seems unlikely that an agent could directly affect ischemia by altering only the level of myocardial metabolism. Collateral flow itself could be altered either indirectly by initiating a coronary steal, as demonstrated for isoproterenol and adenosine, or directly, perhaps by changing coronary perfusion pressure. Future attempts to find therapeutic agents that spare ischemic myocardium should focus on techniques to increase collateral blood flow.

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Preceding His-Atrial Interval As a Determinant of Atrioventricular Nodal Conduction Time in the Human and Rabbit Heart

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This investigation shows that atrioventricular (A-V) nodal conduction time (A-H interval), both in the human and in the isolated rabbit heart, is determined mainly by the length of the preceding His-atrial (H-A) interval. The A-H intervals obtained during atrial extrasystolic stimulation at different basic rates, during Wenckebach cycles and during both transient and steady state responses to stepwise increases in stimulation frequency were plotted against the corresponding H-A intervals. The A-H intervals were found to have nearly the same duration provided they were preceded by the same H-A interval. The only important difference appeared in the short H-A interval range as a shortening of the A-H interval at faster basic rates. This facilitating effect of frequency, which was found in the majority of cases, is compatible with the similarly frequency-dependent shortening of the functional refractory period of the A-V node.

When the preceding atrial interval is used to evaluate the resting period of the atrioventricular (A-V) node, A-V nodal conduction time appears to increase not only with shortening of the preceding cycle but also with cumulative effects of frequency (fatigue).[1,2] One indication of fatigue is that the atrial extrasystole introduced with the same atrial coupling interval is conducted more slowly through the A-V node when the basic rate is faster.[1,2] Also, when the atrial stimulation frequency is suddenly increased, A-V nodal conduction time increases progressively to reach a new stable value only after several beats at the new rate.[2]

As pointed out by Lewis and Master,[3] however, the preceding atrial interval is not a good indicator of the resting period of the A-V conduction system because it does not take into account the changes in conduction time of the basic beat. Because the basic conduction time is prolonged at fast basic rates, the time of onset of the A-V nodal recovery cycle is delayed. Consequently, the conduction time of an extrasystole introduced with the same atrial coupling interval at different basic rates may be longer at fast basic rates simply because the impulse enters the node earlier in its recovery cycle. Lewis and Master[3] considered that the R-P interval (interval between the atrial activation and the preceding ventricular activation) represented more nearly the resting period of the A-V conduction system. This view was also adopted by other electrocardiographers.[4,5] A recent study by Levy et al.[6] provided further evidence that the R-P interval controls the P-R interval. They demonstrated in dogs that there is a causal relation between a given P-R interval and the preceding R-P interval during the Wenckebach cycles.

Earlier, Moe et al.[7] criticized the "sanctity" of the R-P–P-R relation. They claimed that "it is the interval between successive entries of the node rather than the interval between the last emergence and the succeeding entry which determines how facile will be the transit." This opinion was based mainly on the assumption that the delay encountered in the upper node by a premature beat increased with shortening of cycle length. This delay would permit a longer time for recovery in the lower node. Since a recent study[8] demonstrated that no important cycle

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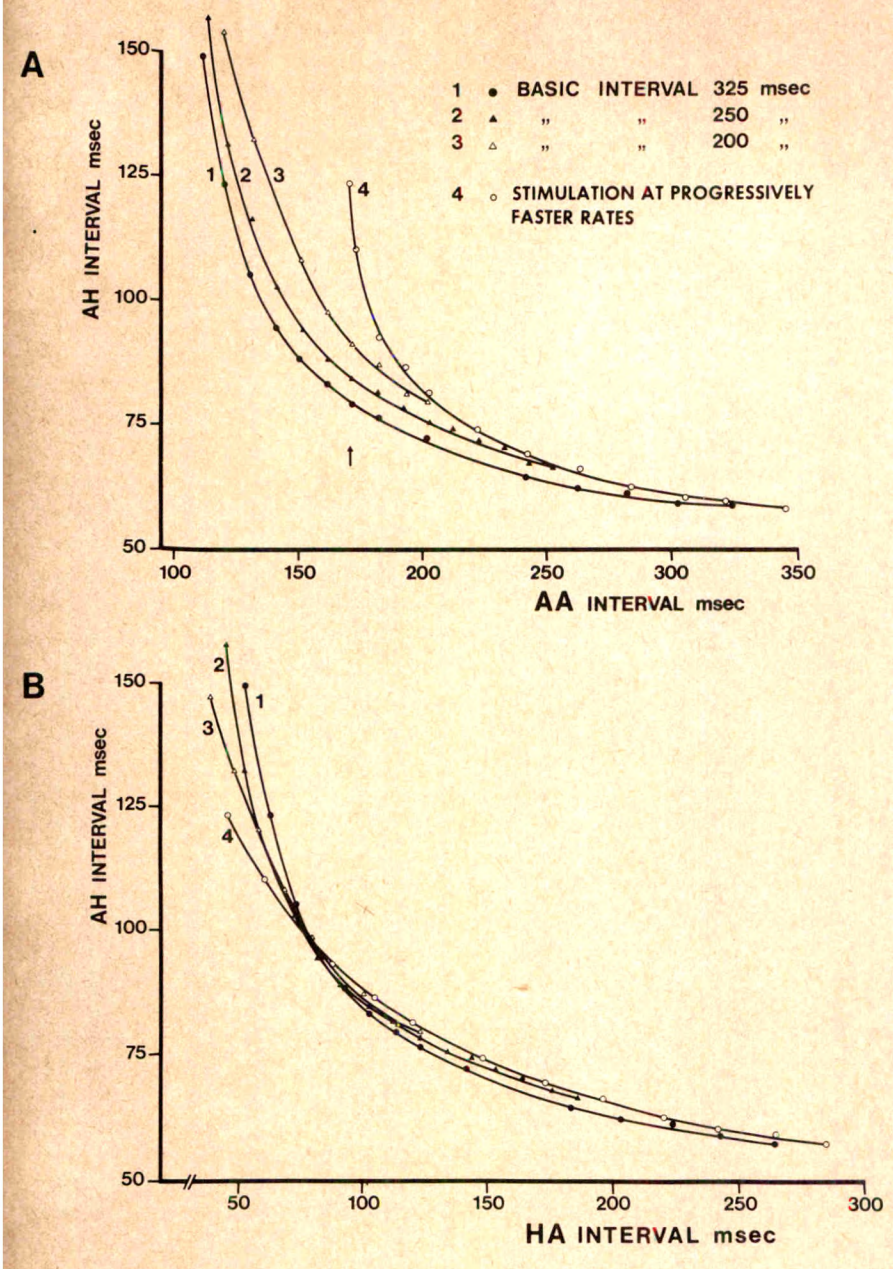


FIGURE 1. A-A plotting **(A)** and H-A plotting **(B)** of A-H intervals obtained in one rabbit heart during the propagation of extrasystolic beats introduced at three different basic rates (curves 1, 2 and 3) and during the steady state of progressively faster rates (curve 4). In the A-A plotting **(A),** conduction times were shifted to the right from curve 1 to curves 2 and 3 by increasing the basic rate from 325 to 250 and to 200 msec periods, respectively. Conduction times were longest for all A-A intervals during stimulation at progressively faster rates (curve 4). Conversely, in the H-A plotting **(B),** there are only minor differences between the four conduction curves. For identical H-A intervals within the range of 80 to 250 msec, the A-H interval is slightly longer at faster basic rates. At H-A intervals shorter than 80 msec, the curve order is inverted. In this range, for an identical H-A interval, the A-H interval is shorter at faster basic rates.

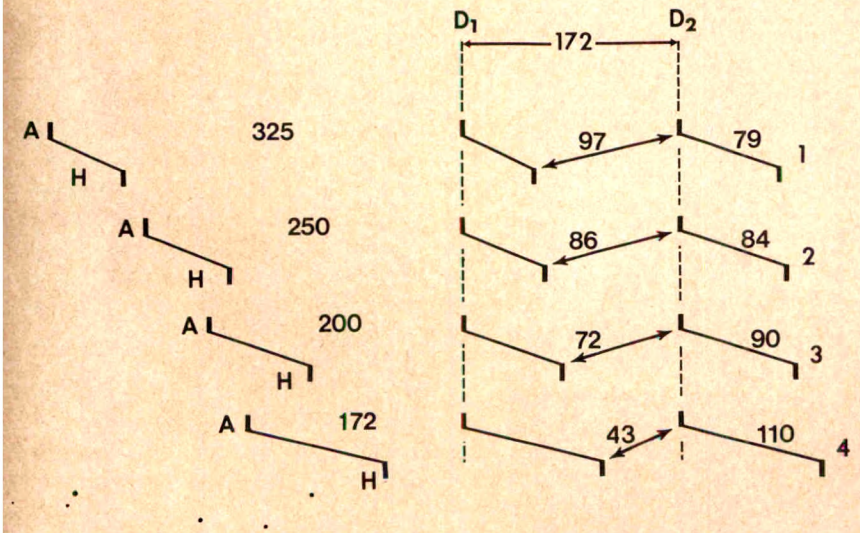


FIGURE 2. Influence of conduction time through the A-V node on the beginning of its resting period. This scheme is a scale reproduction of events recorded in the last two beats preceding the four different A-H intervals indicated by the **vertical arrow in Figure 1A.** These A-H intervals are numbered 1 to 4 at the right of the scheme. They were all preceded by an identical A-A interval of 172 msec. In the scheme, these four A-A intervals coincided vertically (**dotted lines** D_1 and D_2). At the left of D_1 are the corresponding last basic A-A intervals. The four different A-H intervals (right of D_2) are preceded by four different values of H-A intervals (**oblique double arrows** at the left of D_2). As the H-A interval decreases, the A-H interval increases. This decrease in H-A interval is secondary to the increase in basic A-H interval (right of D_1), itself due to the decrease of the basic A-A interval (left of D_1).

length-dependent increase in A-V nodal delay takes place in the upper node, this assumption might be questioned.

We therefore reassessed this problem using the His-atrial (H-A) interval as an indicator of the resting period of the A-V node. For this purpose, the A-H intervals produced in human and rabbit hearts with different stimulation patterns were plotted against their preceding H-A intervals. The results indicate that for an identical H-A interval, A-V nodal conduction time is nearly the same regardless of the stimulation pattern used.

Methods

Rabbit Heart

The heart was excised from rabbits anesthetized with sodium pentobarbital (20 mg/kg body weight intravenously) and was dissected according to the method of Hoffman et al.[9] The resulting preparation contains the right atrium with the sinus node, the interatrial septum, the atrioventricular (A-V) ring and part of the interventricular septum. The preparation was mounted in a tissue bath[10] through which a modified Tyrode solution equilibrated with a mixture of 95 percent oxygen and 5 percent carbon dioxide was circulated. Temperature was maintained at 37° C ± 0.5° C (range of variation) and pH was maintained at 7.35.

Extracellular activity was recorded with bipolar electrodes placed on the crista terminalis and on the His bundle. The preparation was stimulated by means of rectangular current pulses (2 × threshold, 2 msec duration) passed through a bipolar stimulating electrode placed in the sinus nodal region.

After the electrodes had been positioned, the atrium was driven with a stimulation period 20 msec shorter than the spontaneous sinus period. The preparation was then allowed to stabilize and was considered stable when the time from the stimulus to the His complex, as monitored on the oscilloscope, remained constant for 10 minutes. The following stimulation patterns were applied to seven preparations: First, an extrasystolic pulse was introduced at every 10th basic beat according to the method of Krayer et al.[11] The extrasystolic coupling interval was shortened progressively until A-V nodal propagation failed. The same procedure was repeated at two faster basic rates. Finally, the preparation was submitted to progressively faster driving rates until 1:1 A-V nodal propagation failed and Wenckebach cycles occurred. In the latter mode of stimulation, each rate was maintained for about 20 seconds. The measurements were made after 15 seconds at the new rate. The whole procedure lasted less than 15 minutes. In two preparations, the atrium was submitted to extrasystolic stimulation only at the basic driving rate and to successive stepwise increases in driving rate. In the latter mode of stimulation, 15 beats of the basic driving rate alternated with 15 beats of a faster rate. This alternation resulted in a series of responses during which transient changes secondary to increased frequency could be studied.

Measurements: Recordings were made on a tape recorder at a speed of 15 inches (38 cm)/sec. For time measurements the tapes were played back at 1,875 inches (4,763 cm)/sec and the complexes written on an Elema ink-writer polygraph at 120 mm/sec, allowing a time resolution of 1 msec. All measurements reported were taken from the atrial (A) and the His (H) complexes in the His bundle electrogram. The timing of A and H was measured from the first rapid deflection of these complexes. The A-A interval was defined as the interval between two consecutive A complexes on the His electrogram. The H-A interval was defined as the interval between the preceding H complex and the actual A complex in the His lead. The functional refractory period of the A-V node was defined as the shortest H-H interval obtained by atrial extrasystolic stimulation. The effective refractory period of the A-V node was defined as the shortest interval between two atrial impulses propagated to the His bundle.

Human Heart

Records from nine patients thought to have A-V conduction abnormalities but later found normal were selected retrospectively. A His bundle electrogram had been recorded in all these patients during extrasystolic stimulation at different basic rates and during regular stimulation at progressively faster rates. From the His electrogram, the A-A, A-H, H-A and H-H intervals were determined for the extrasystolic beats and for the steady state of the progressively faster rates. These intervals were defined and measured as in the rabbit.

A tripolar catheter was used to record the electrogram of the His bundle.[12] A bipolar catheter was used for stimulation of the right atrium. Pulse intensity was twice threshold; pulse duration was 2 msec. Other electrograms included leads I, II, III, V_1, V_3 and V_6 as well as a bipolar atrial electrogram. The electrograms were recorded simultaneously on paper and tape.

Results

Extrasystolic stimulation and regular stimulation at different rates: A-H intervals were obtained in seven isolated preparations from rabbit hearts during atrial extrasystolic stimulation at three different basic rates and during the steady state of progressively faster rates. Each of these A-H intervals was plotted against both its preceding A-A interval (A-A plotting) and its preceding H-A interval (H-A plotting) (Fig. 1). For identical preceding A-A intervals, extrasystoles were conducted with longer A-H intervals at faster basic rates (Fig. 1A). The A-H intervals obtained during the steady state at the progressively faster rates were at all A-A intervals longer than those obtained during extrasystolic stimulation. This frequency-dependent shift of the conduction curve was observed in all seven preparations. This phenomenon has been previously observed in dogs and attributed to a cumulative effect of frequency on conduction time (fatigue).[1,2,13]

An increase in the A-H interval, however, shortened the next H-A interval and therefore curtailed the resting period of the node (Fig. 2). Thus the extrasystolic A-H interval might be prolonged at faster basic rates for the simple reason that the test impulse enters the node earlier in its recovery cycle under these conditions. This fact was thought to be responsible for an important part of the frequency-dependent shift of the curves in Figure 1A. To compare conduction times through the node for identical resting periods, each A-H interval in Figure 1A was plotted against its corresponding H-A interval. In the H-A plotting (Fig. 1B), the four curves appeared closely related. The A-H intervals obtained with the different stimulation patterns were comparable provided they were preceded by similar H-A intervals. The reduced difference between curves 1 and 4 in the H-A plotting is particularly striking. This clustering in the H-A plotting was found in all seven preparations.

Two frequency-dependent shifts in the conduction curves persisted in the H-A plotting. The first appeared as an upward shift of the curves at intermediate and long H-A intervals (Fig. 1B). In this range, for an identical H-A interval, the A-H interval was slightly longer if the basic rate was faster. This shift was small but was consistently present in the seven preparations (range 2 to 5 msec with a mean ± standard error of 3.7 ± 0.5 when measured at its maximum). The second difference, observed in five of seven preparations, was a leftward and downward shift of the curves at short H-A intervals. In the short H-A interval range, the curves in Figure 1B have an inverted order compared with the curves in Figure 1A. In this range, for the same H-A interval, the A-H interval is shortest at the fastest rate. The quantitative determination of this effect is complicated by the fact that the minimal H-A interval resulting in A-V propagation varies with the stimulation pattern. However, by taking for comparison the minimal H-A interval for which an A-H interval was obtained with each stimulation pattern, it was found that the frequency-dependent decrease in A-H interval was 18 ± 5.1 (range of 7 to 30 msec). In these five preparations, the functional refractory period of the A-V node was shortened by an average of 11 msec at the fastest basic rates. In the other two preparations, the rightward shift of the conduction curves persisted even in the short H-A interval range; here the functional refractory period of the A-V node increased with frequency. There was no consistent relation between rate-dependent changes in the A-H interval and rate-dependent changes in the value of the effective refractory period of the node.

Wenckebach cycles: The A-H–H-A interval relation was also examined in successive beats of Wenckebach cycles produced by rapid atrial driving. In such a sequence (Fig. 3A) the H-A interval diminished from beat to beat and the A-H interval increased accordingly. Furthermore, when each A-H interval was plotted against its corresponding preceding H-A interval (Fig. 3B), the resulting marks on the graph fell into the same range of values as those obtained with extrasystolic stimulation in the same preparation. It is also obvious

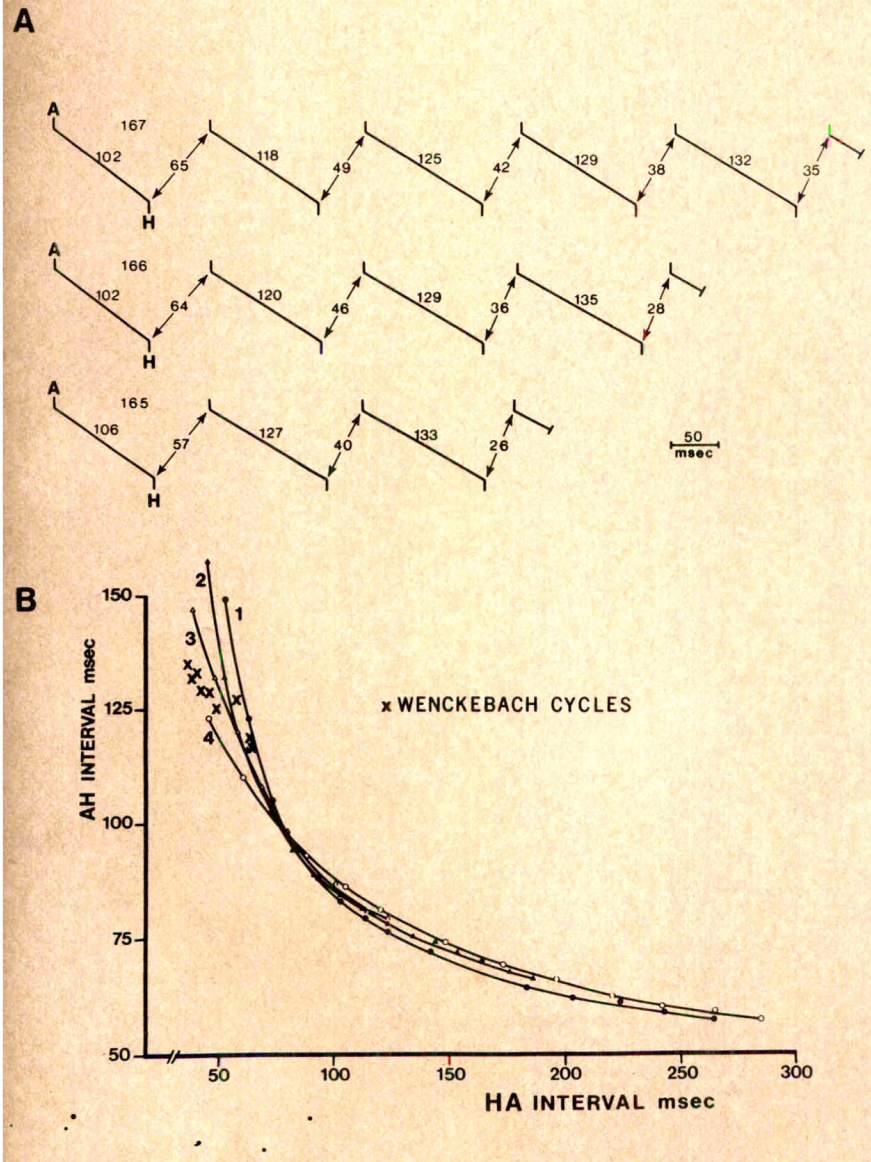


FIGURE 3. A-H–H-A interval relation during Wenckebach cycles in the same rabbit heart as that from which data of Figure 1 were obtained. The three schematic strips seen in **A** are scale reproductions of three different Wenckebach cycles obtained a few seconds later by driving the atrium at 167, 166 and 165 msec, respectively. In the three Wenckebach cycles, as the H-A interval **(oblique double arrows)** decreases the next A-H interval is lengthened, which in turn causes further shortening of H-A interval until block occurs. In **B**, the A-H and H-A intervals shown in **A** were plotted **(crosses)** on the same graph as that illustrated in Figure 1B. The A-H intervals in Wenckebach cycles **(crosses)** fell in the area delineated by the upper range of conduction curves obtained with other modes of stimulation.

that the H-A interval preceding the blocked beat in these three Wenckebach cycles (Fig. 3A) was shorter than those compatible with conduction as determined by extrasystolic stimulation (Fig. 3B).

Step responses: The A-H–H-A interval relation was also examined during transient responses to stepwise increases in stimulation frequency (Fig. 4). After a sudden increase in frequency, the A-H interval increased progressively as the H-A interval diminished. Both the A-H and H-A intervals reached stable values at the same beat number. This steady state was reached within two beats in step 1 but was not yet completely

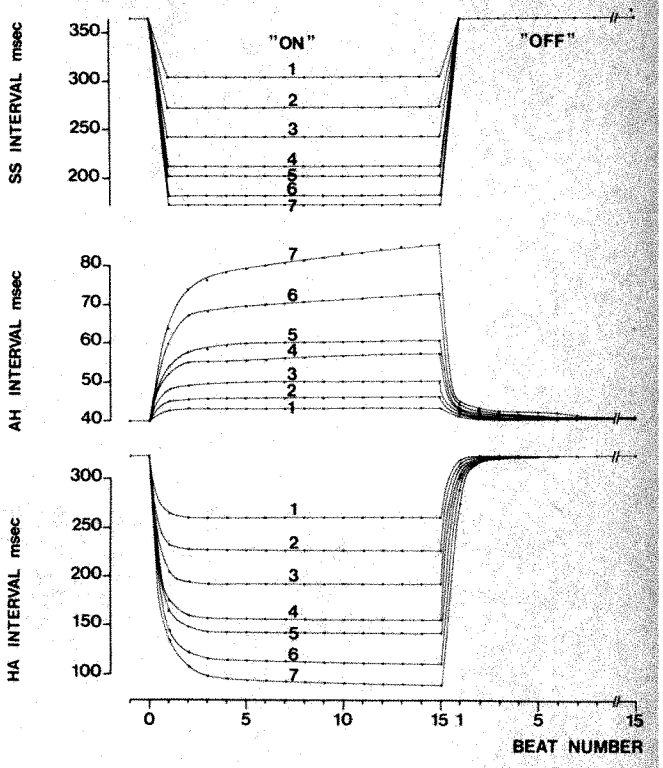


FIGURE 4. A-V nodal transient responses obtained in one rabbit heart submitted to seven different stepwise increases in atrial driving rates (S-S). These responses were superimposed on this graph by plotting for each of them, the S-S, A-H, and H-A intervals according to the beat number at the top, middle and bottom of the graph, respectively. Each number 1 to 7 appearing in a vertical row refers to these variables for one step. On the top, the S-S interval was decreased by 60 msec in step 1 and progressively more in succeeding steps. The S-S interval was 172 msec in step 7. "On" therefore indicates the 15 beats of the faster rate and "off" the following 15 beats of basic rate. In each step, changes in the A-H interval are inversely related to changes in the H-A interval, both variables reaching stable values at the same beat number. The A-H and H-A intervals reach stable values more rapidly during the "off" than during the "on" responses.

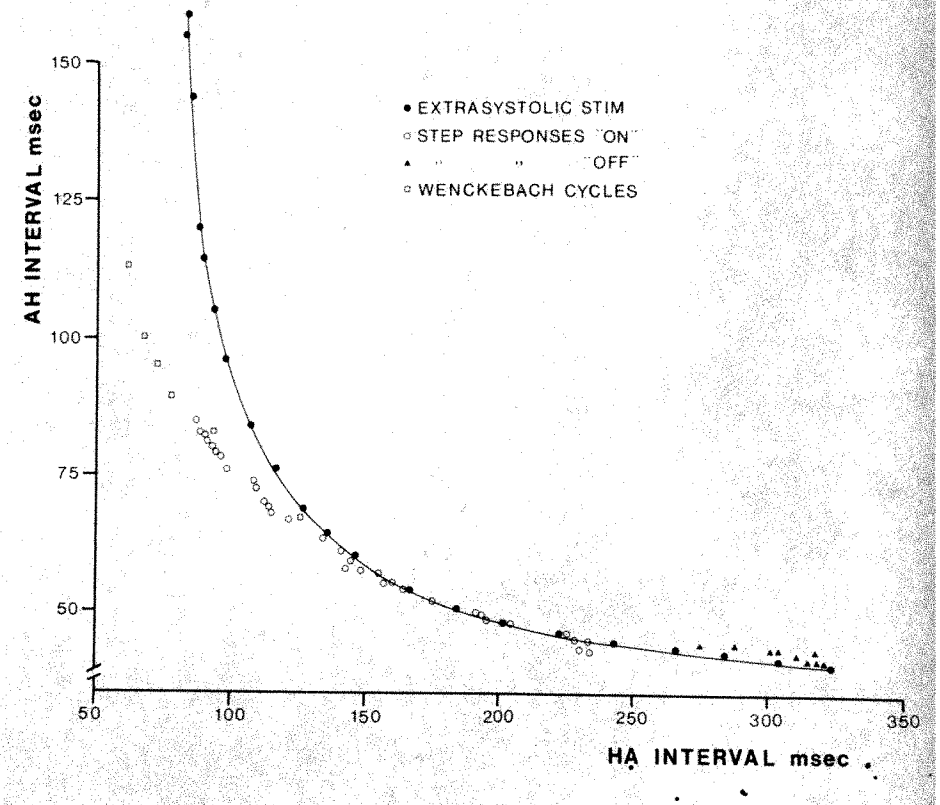


FIGURE 5. A-H–H-A interval relation during step responses, extrasystolic stimulation (STIM) and Wenckebach cycles in one rabbit heart. For the step responses, which correspond to those illustrated in Figure 4, only each different value of the A-H–H-A relation is plotted. Because the same relation persisted for several beats at steady states, the number of open circles and triangles is limited. For identical H-A intervals of 100 to 325 msec, the A-H intervals have nearly identical values regardless of the stimulation pattern used. However, for H-A intervals shorter than 100 msec, the A-H intervals obtained with extrasystolic stimulation are longer than those obtained in the other two circumstances.

reached after 15 beats in step 7. With the return to basic cycle length ("off" responses), the return to the basic A-H interval occurred within a few cycles as did the H-A interval (Fig. 4). Only after the fastest rate (step 7) was the A-H interval delayed in its return to the basic value. However, this delay persisted for only a few beats and was less than 3 msec (Fig. 4, middle right).

The A-H–H-A interval relation obtained during the step responses was compared with that obtained from the same preparation during extrasystolic stimulation at a slow basic rate and during Wenckebach cycles (Fig. 5). Under these very different conditions of A-V propagation, the A-H–H-A relation was nearly identical over most of the H-A interval range. Only in the very short H-A interval range were A-H intervals shorter during step responses and during Wenckebach cycles than during extrasystolic stimulation.

The A-V node operated in two different ranges of H-A intervals during the "on" and "off" responses (Fig. 4 and 5). For the "on" responses, the H-A interval shortened from 250 to 85 msec; for the "off" responses, it lengthened from 275 to its control value of 325 msec. In the latter range, the A-H–H-A interval relation is on the flat part of the curve. The A-H interval returns rapidly to its control value and so does the H-A interval. Conversely, the curve becomes steeper as the H-A interval becomes shorter. An increase in rate causes a sudden decrease in the H-A interval, which causes the next A-H interval to increase, which further shortens the next H-A interval, and so on. For a large rate increase, several cycles are therefore necessary to reach a new steady state. This observation explains the difference in the number of beats necessary to reach stable values of A-H intervals in these two types of responses.

The A-H–H-A relation in man: The A-H–H-A interval relation was also examined retrospectively in nine human tracings obtained during endocavitary investi-

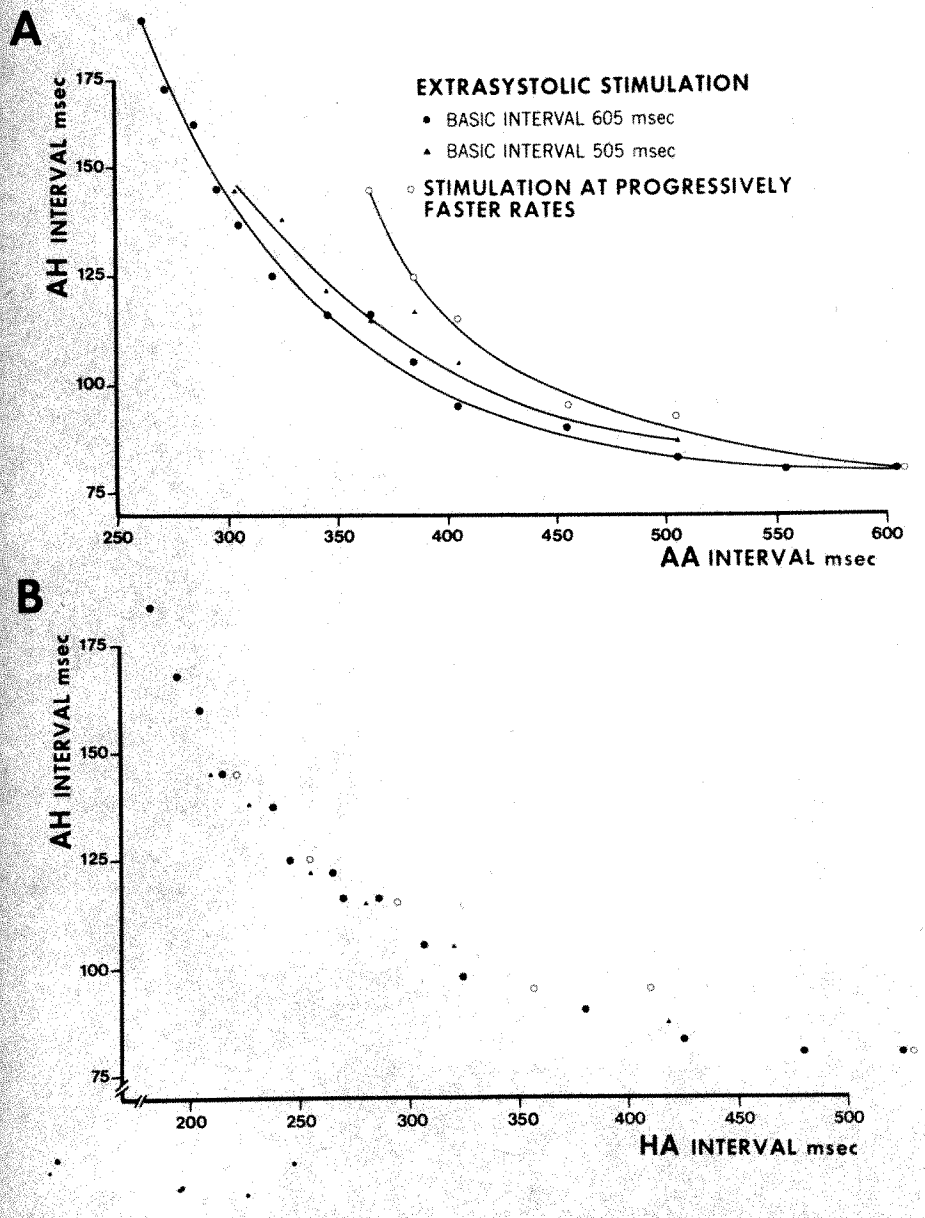


FIGURE 6. A-A plotting **(A)** and H-A plotting **(B)** of A-H intervals found in one man during endocavitary investigation of A-V conduction. As indicated by the symbols in the insert, the three different curves in **A** correspond to the A-H intervals obtained during extrasystolic stimulation at two different basic rates and during the steady state following each increase in stimulation frequency. The A-A plotting **(A)** shows a clear rightward and upward shift of the conduction curves under the influence of increased frequency. Conversely, in the H-A plotting of the same A-H intervals **(B)**, there is no distinct difference between the A-H intervals obtained in these three circumstances.

gation of suspected but unconfirmed A-V conduction abnormalities. The A-H intervals obtained during extrasystolic stimulation at different basic rates and during the steady state of each progressively faster rate of stimulation were plotted against both the preceding A-A and H-A intervals. In five of the nine patients, the difference between the conduction curves was less when the A-H intervals were plotted against the H-A as compared with the A-A interval (Fig. 6). Thus, for the same H-A interval, atrial impulses were conducted similarly through the A-V node regardless of the previous history of the node. In two of these five patients, some frequency-dependent shifts of the A-H intervals persisted in the H-A plotting. Under cumulative effects of frequency, the A-H intervals were slightly increased in the intermediate and long H-A interval ranges, whereas they were shortened in the short H-A interval range.

In the remaining four patients, uncontrolled variations in A-H intervals did not permit evaluation of the frequency-dependent shift. These variations can probably be accounted for by extrinsic influences modulating A-V conduction in man.

Discussion

H-A interval as determinant of A-V conduction time: It seems evident from these results that the preceding H-A interval is the important determinant of the time an impulse takes to travel through the A-V node. This view is supported by the fact that, regardless of the stimulation pattern used, the A-H intervals were surprisingly similar provided they were preceded by the same H-A interval. The desirability of using the length of the H-A interval to measure the resting period of the A-V node is supported by its relative accuracy in evaluating the time of arrival of the atrial impulse in the nodal recovery cycle. Because the A-A interval is less accurate in this respect (Fig. 2), a large part of the shift of the conduction curves on the A-A plotting observed in this study and others[1,2,13] is artificial. In other words, for the same atrial interval, the extrasystolic A-H interval increases at faster basic rate not because of cumulative effects of frequency but because the A-V node is activated sooner after the end of its refractory period. The use of the H-A interval eliminates this measuring error.

The H-A interval must nevertheless be considered an indicator rather than an exact measurement of the time of arrival of the atrial impulse in the nodal recovery cycle. The H-A interval preceding a given atrial beat includes neither the time elapsed in activation of NH cells before the occurrence of the H complex in the preceding beat, nor the time elapsed after the A complex for the activation of late AN cells of the node in the considered beat. These two values should be added, respectively, at the left and right ends of the H-A interval in order to obtain the exact value of the phase of excitability at which the impulse enters the delay-producing part of the node. However, because AN and NH cell activation times were shown to be cycle length-independent, at least in the range of A-A intervals for which A-V conduction is successful,[8] the H-A interval underestimates the resting period of the node by a constant value. This value may therefore be neglected when considering A-H interval changes. For the same reason, the fact that the A complex in the His electrogram is probably a marginal sample from a broad activation front would not interfere with the accuracy of the measurements. The use of this A complex aids in eliminating the influence of atrial factors on A-H interval measurement.[14]

Cumulative effects of basic atrial rate: When Lewis and Master[3] plotted extrasystolic P-R intervals obtained at different basic rates against the corresponding R-P intervals, they observed two types of cumulative effects of frequency. In the long R-P interval range, the increased basic rate caused a slight lengthening of the extrasystolic P-R interval, thus an impairing cumulative effect of frequency that they called "fatigue." Conversely, in the short R-P interval range, a frequency-dependent shortening of the extrasystolic P-R interval was observed. This facilitating effect was attributed to a shortening of the refractory period. The cumulative effects of frequency observed in the present study (Fig. 1B and 5) were qualitatively similar. In summary, at intermediate and long H-A intervals, conduction was very slightly impaired whereas it was facilitated at short H-A intervals by cumulative effects of frequency. Thus, use of the His bundle electrogram permitted a more specific evaluation of the role of the A-V junction in these cumulative effects of frequency. However, because an A-A interval encompasses an A-H and a H-A interval, it may be suggested that the influence of the encompassed A-H interval is negated by the H-A interval. With regard to a previous study from this laboratory[15] showing that the interval after which an (n + 1)th atrial beat will be propagated depends only on the conduction time of the nth beat and not on the previous history of the A-V conduction system, this possibility assumes particular importance. The present study confirms that the conduction time of the nth beat may have an important influence on conduction time of the (n + 1)th beat but shows that this influence occurs through a change in the resting period of the node rather than as a direct influence of conduction time itself. If the node is allowed the same time to recuperate (same H-A interval), it will conduct the impulse with the same A-H interval, within narrow limits, regardless of its previous history. This previous history includes that of the nth beat. Thus the influence of the A-H interval of the preceding beat is not negated by the H-A interval but evaluated with respect to the resting period of the node.

These observations might help to explain the apparent contradiction between the effects of frequency on the functional refractory period and conduction time in the A-V node. Many investigators have reported[1,13,16–18] that, under the cumulative effects of frequency, conduction time is prolonged but the functional refractory period is shortened. If the A-V conduction time is shortened by the cumulative effect of frequency, as it appeared to be in the short H-A interval

range, the frequency-dependent shortenings both of the refractory period and of conduction times are parallel and consequent.

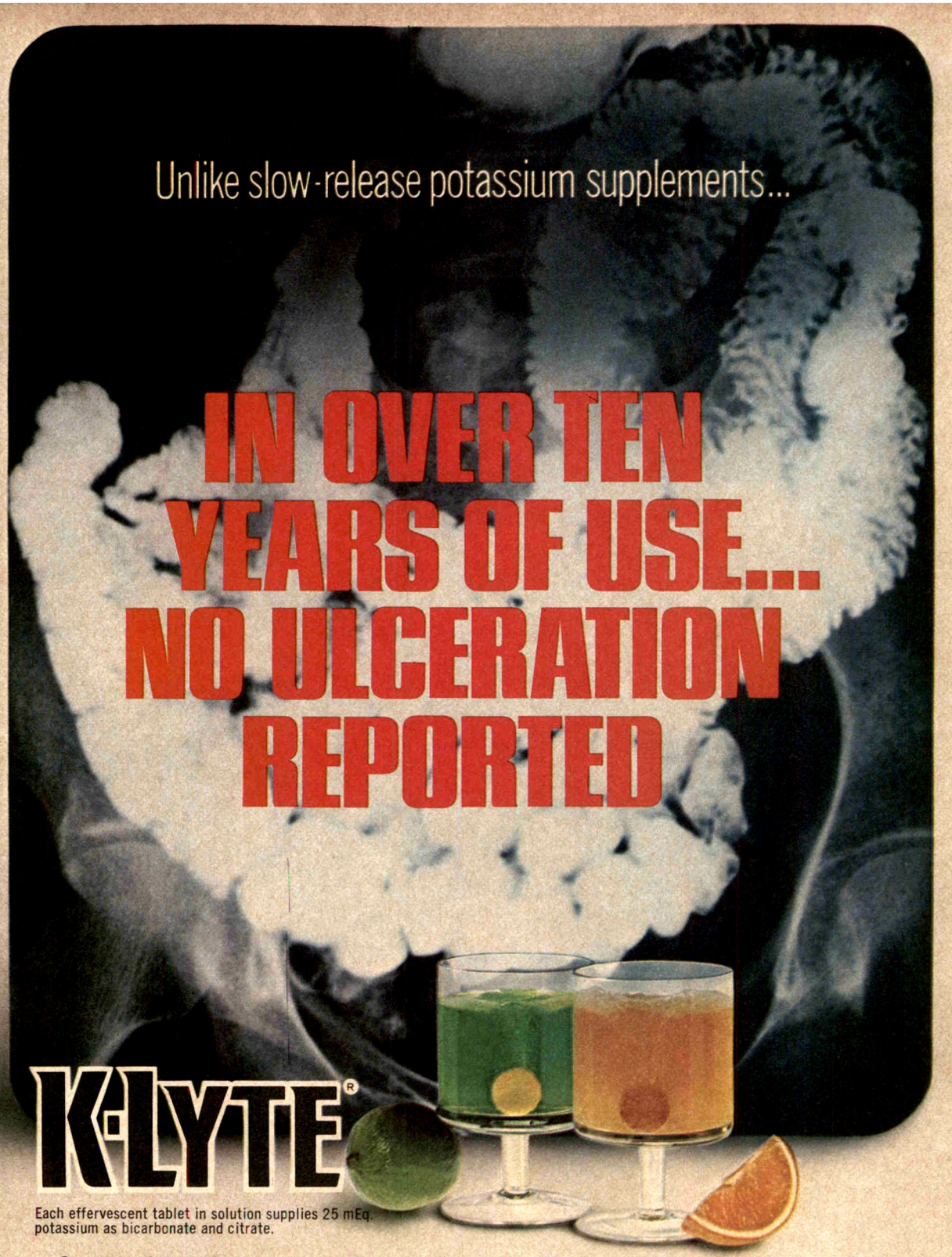
The results of this investigation may be summarized as follows: (1) Conduction time through the A-V node both in the human and the rabbit heart depends mainly upon the length of the preceding H-A interval. (2) This relation holds true both for steady and transient states of A-V nodal conduction. (3) If one takes the H-A interval as an indicator of the resting period of the A-V node, A-V nodal conduction appears to be only slightly influenced and mainly facilitated by the cumulative effects of frequency.

Acknowledgment

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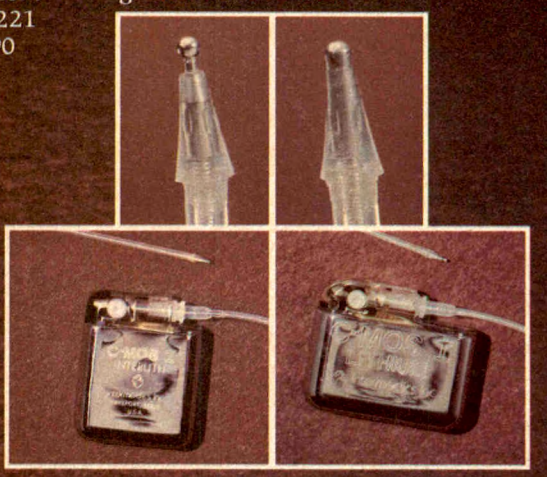
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Intermedics' lithium pulse generators provide proven long-term, trouble-free operation and the low power consumption of C-MOS I circuitry combined with the superior life expectancy of a lithium battery hermetically sealed in its own container. Each pulse generator is also hermetically sealed in its own tissue-compatible, interference-resistant 316L stainless steel container, which features smoothly rounded edges for greatest patient comfort. Intermedics offers two excellent models: the original Model 221 *C-MOS I Lithium* weighing 90 grams (6.3 cm by 3.8 cm by 1.8 cm); and the new Model 223 *Interlith*™, weighing just 65 grams (5.5 cm by 4.2 cm by 1.4 cm). Both are available in demand or continual modes, with assured power life expectancies in excess of 6 years. Pre-set stimulation rates are available from 60 to 100 pulses per minute.

System Part 2: The Leads

Intermedics' pulse generators are designed to accept most competitors' leads. However, Intermedics manufactures a series of non-corroding, platinum-tipped leads which provide low stimulating and sensing thresholds and are designed in every way to increase the power life expectancy of Intermedics' pulse generators. Closed coil construction resists dislodgment and prevents lead fractures. Model 461 features a cylindrical tip, and the newer Model 463 offers a spherical tip for greater surface area.



System Part 3: Trace-A-Pace™ Remote Monitoring

Intermedics is the only pacemaker manufacturer on the market which provides a remote monitoring service at no additional charge with each implanted pulse generator. At the request of the patient's physician, the patient is provided with a lightweight, easy-to-use, portable transmitter. At any time, from any telephone, he can transmit his pulse and pacer rhythm to Intermedics. He simply attaches color-coded, dry electrodes, dials a toll-free telephone number, and places the telephone receiver on his transmitter. Intermedics will receive and record the rhythm strip and pulse generator rate. If any irregularity is observed, the patient's physician will be contacted immediately. With each transmission, the physician will receive a report and a copy of the rhythm strip, greatly reducing the time required for patient follow-up, and increasing the patient's confidence and mobility.

System Part 4:
Your Intermedics Representative

All Intermedics representatives are on call 24 hours a day. When necessary, they can have any Intermedics component or an entire Intermedics Lithium Pacemaker System in your hands shortly after you call.

For the location of your nearest Intermedics representative or additional information about our products, call toll-free 800-231-2330. In Texas call collect 713-233-8611.

Intermedics Inc.

P. O. Box 617 Freeport, Texas 7754

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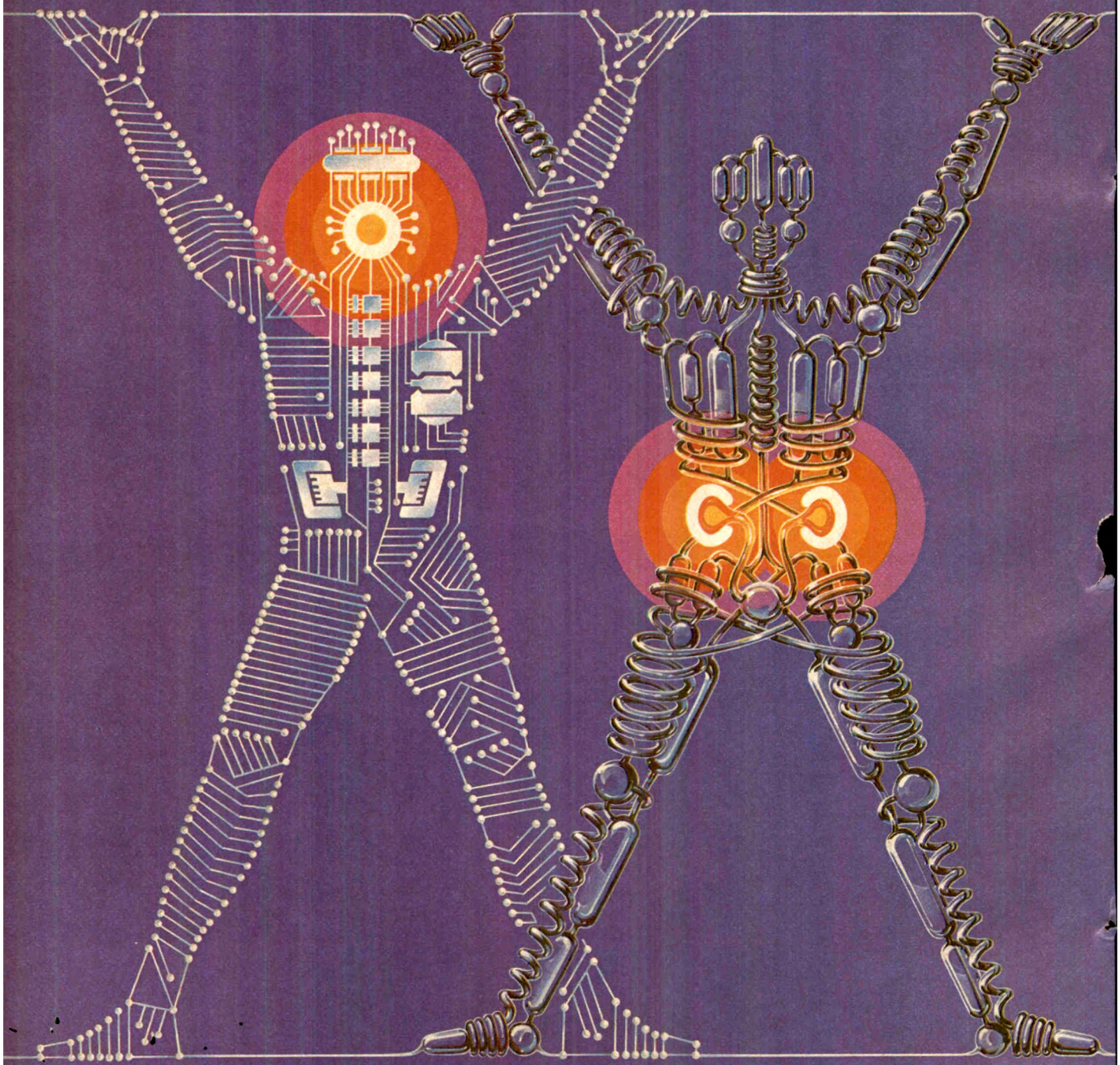
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Combipres®

.1 and .2

Each tablet contains:
Catapres®, brand of clonidine hydrochloride,
0.1 or 0.2 mg and chlorthalidone, 15 mg

The only major new combination antihypertensive in a decade



Please see brief summary of the prescribing information including precautions, warnings, adverse reactions.

nonreserpine

Combipres® 1 and 2

Each tablet contains:
Catapres® brand of clonidine hydrochloride, 0.1 or 0.2 mg and chlorthalidone, 15 mg

Works better than either component in equivalent doses*

Works in mild to severe hypertension

Works conveniently for patients who need more than one drug*

Works for less than the cost of separate Rxs*

Works and works and works—convenience and economy promote long-term patient compliance

*Combipres is not indicated for initial therapy of hypertension. It is indicated for hypertensive patients who need more than one drug for adequate lowering of blood pressure and who have proved to be responsive to its components given separately in dosages equivalent to those in the combination.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

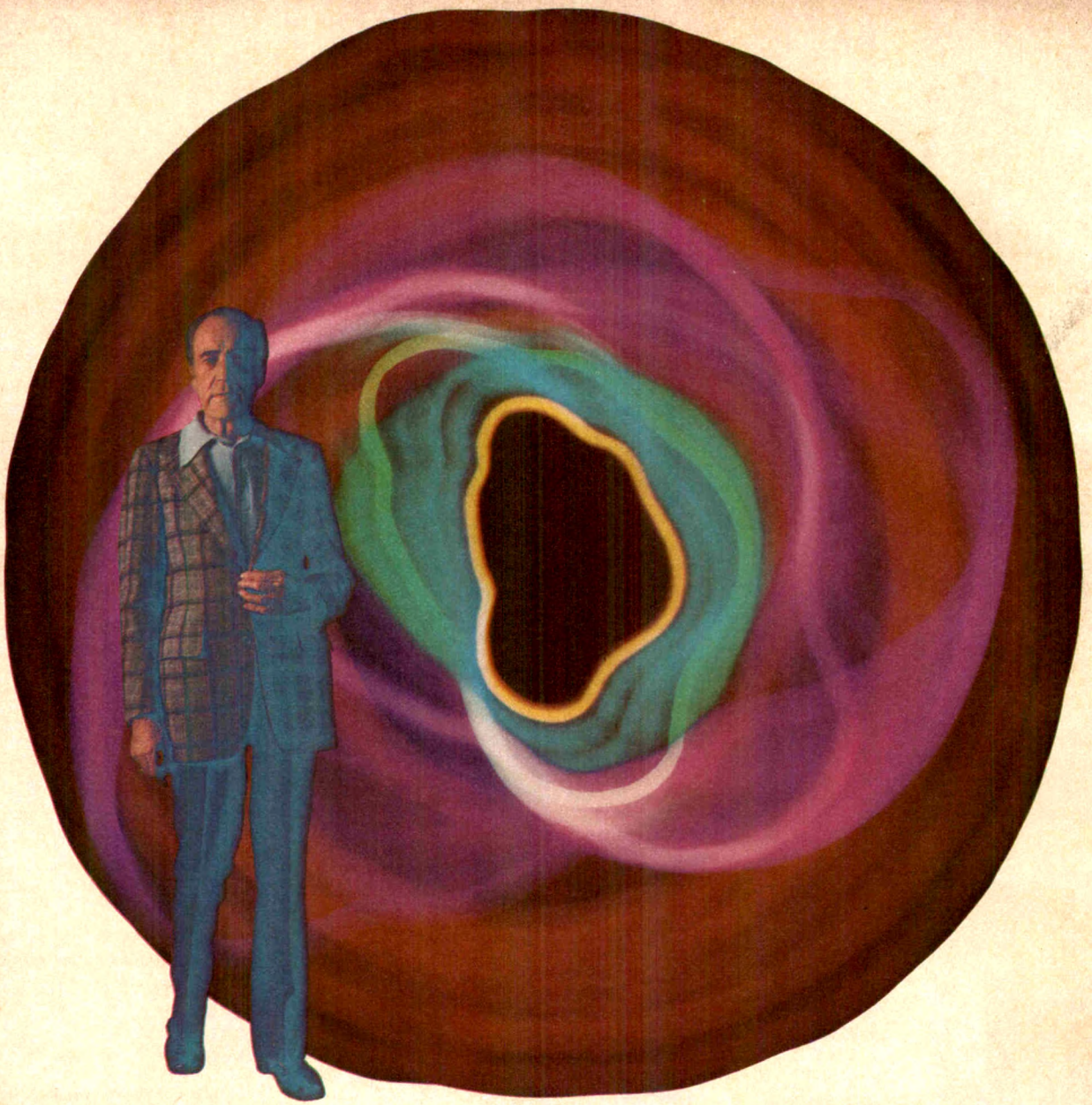
How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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Arlidin® 6 mg.
(nylidrin HCl)
Vasodilator/Vasorelaxant

Where there is a vasospastic component to vascular disease*

Helps increase blood supply
Acts directly at the arteriolar wall to relieve vasospasm associated with sclerotic disorders *

Maintains mean arterial blood pressure
No postural hypotension reported in over a decade of use†

Encourages patient activity
Symptomatic improvement through relief of vasospasm may enhance ability to function

Usual dosage: 6 mg. t.i.d. for at least 4 weeks titrating to 12 mg. t.i.d. or q.i.d. if necessary

†See Adverse Reactions section in Brief Summary

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

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True False

2) The complications of pacemaker electrode placement can be significantly reduced by right ventricular apex angiography.

True False

3) Paradoxical motion of the ventricular septum is commonly seen in patients with atrial septal defects.

True False

4) Which of the following is correct:

A) High-grade obstructive coronary artery disease generally precedes myocardial infarction.
B) High-grade obstructive coronary artery disease generally follows myocardial infarction.
C) The matter is still debatable.

ANSWERS:
1) False; 2) True; 3) True; 4) C

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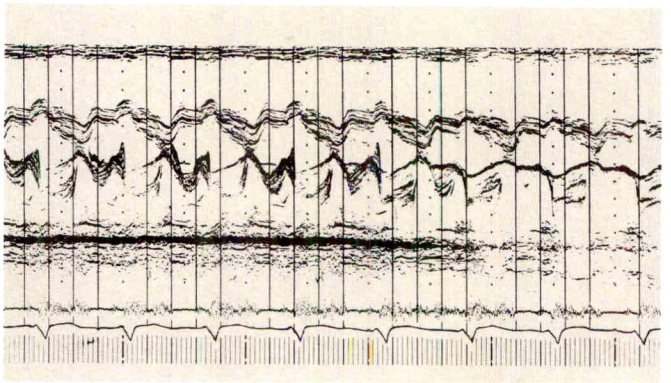
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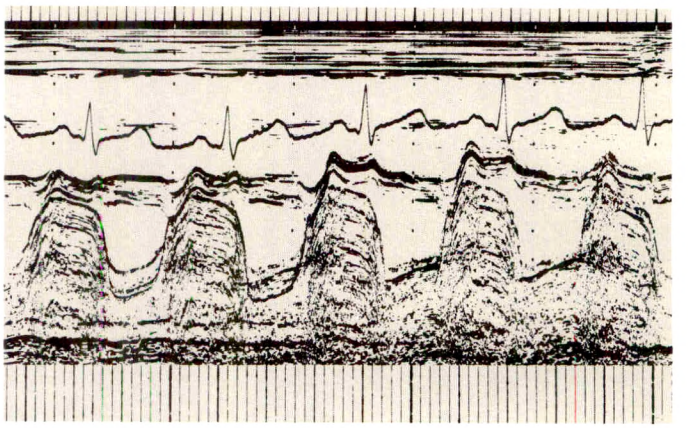
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Flail mitral valve leaflets secondary to bacterial endocarditis. Courtesy Dr. Raymond Gramiak, Strong Memorial Hospital, Rochester, New York.



Left atrial myxoma. Courtesy Dr. Roberta Williams, Children's Hospital Medical Center, Boston, Mass.

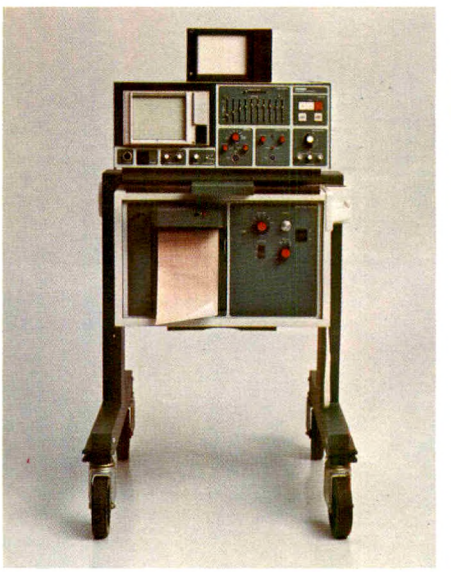
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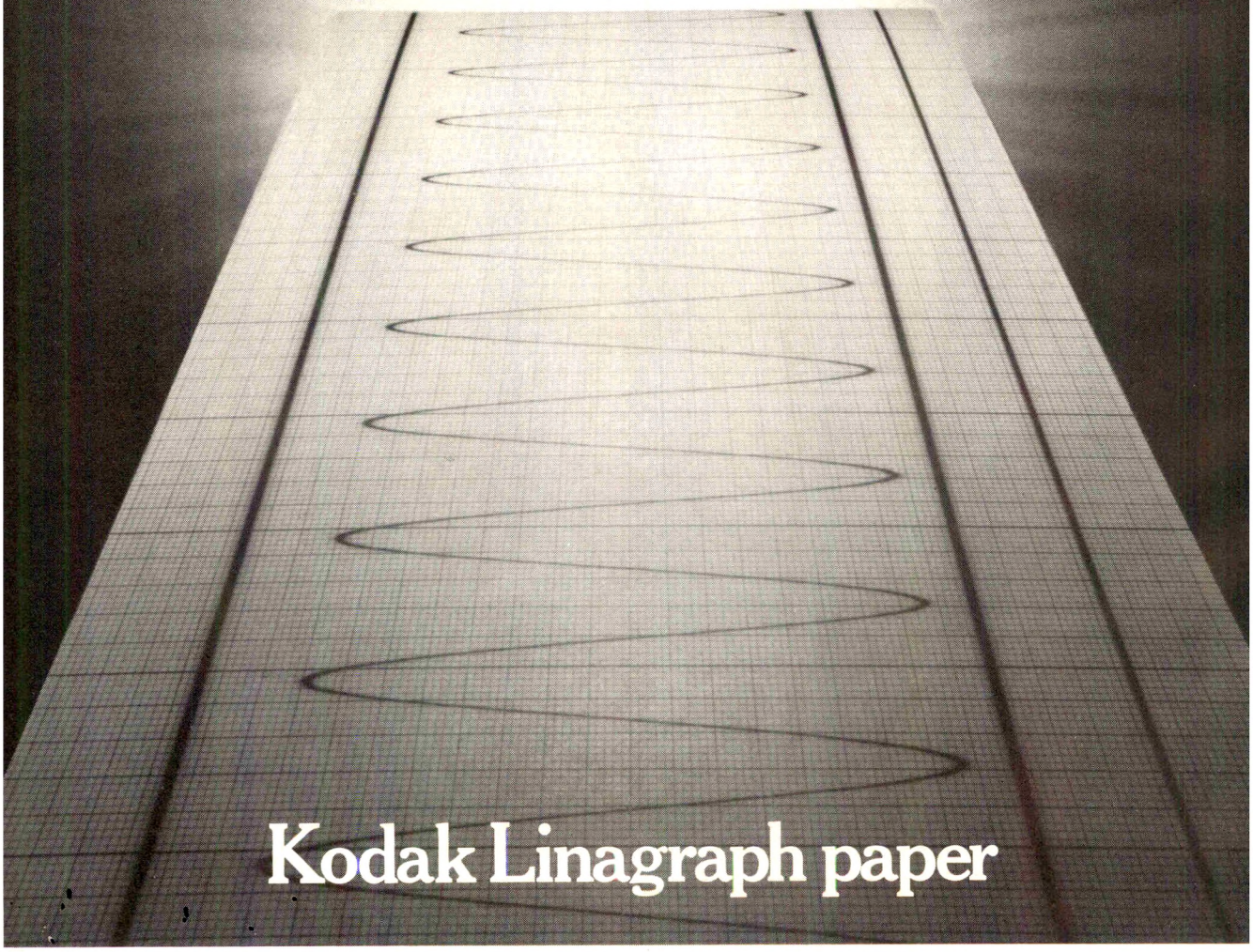
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TABLETS, 250 mg and 500 mg ORAL SUSPENSION, 250 mg per 5 ml

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Because the thiazides have a vital role at the start of antihypertensive therapy and as a part of later steps in therapy in combination with other agents, when necessary—consider DIURIL, the thiazide that started the thiazides.

Contraindicated in anuria and hypersensitivity to chlorothiazide or other sulfonamide-derived drugs. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease, impaired hepatic function, or progressive liver disease.

Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy.

DIURIL...a long, impressive record in the management of hypertension

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...a long, impressive record in the management of hypertension



Contraindications: Anuria; hypersensitivity to this or other sulfonamide-derived drugs.

Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Read circulars for lithium preparations before use of such concomitant therapy.

Use in Pregnancy: Thiazides cross placental barrier and appear in cord blood; in pregnancy, weigh anticipated benefit against possible hazards to fetus, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides appear in breast milk; if use of drug is deemed essential, patient should stop nursing.

Precautions: Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroid or ACTH therapy, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: *Gastrointestinal System*—Anorexia; gastric irritation; nausea; vomiting; cramping; diarrhea; constipation; jaundice (intrahepatic cholestatic jaundice); pancreatitis; sialadenitis.

Central Nervous System—Dizziness; vertigo; paresthesias; headache; xanthopsia.

Hematologic—Leukopenia; agranulocytosis; thrombocytopenia; aplastic anemia.

Cardiovascular—Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).

Hypersensitivity—Purpura; photosensitivity; rash; urticaria; necrotizing angiitis (vasculitis) (cutaneous vasculitis); fever; respiratory distress including pneumonitis; anaphylactic reactions.

Other—Hyperglycemia; glycosuria; hyperuricemia; muscle spasm; weakness; restlessness; transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: When used with other antihypertensive drugs, careful observations for changes in blood pressure must be made, especially during initial therapy. Dosage of other antihypertensive agents must be reduced by at least 50 percent as soon as this drug is added to the regimen. As blood pressure falls under the potentiating effect of this agent, further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary.

How Supplied: Tablets containing 250 mg chlorothiazide each in bottles of 100 and 1000 and single-unit packages of 100; Tablets containing 500 mg chlorothiazide each in bottles of 100, 1000, and 5000 and single-unit packages of 100; Oral Suspension containing 250 mg chlorothiazide per 5 ml in bottles of 237 ml.

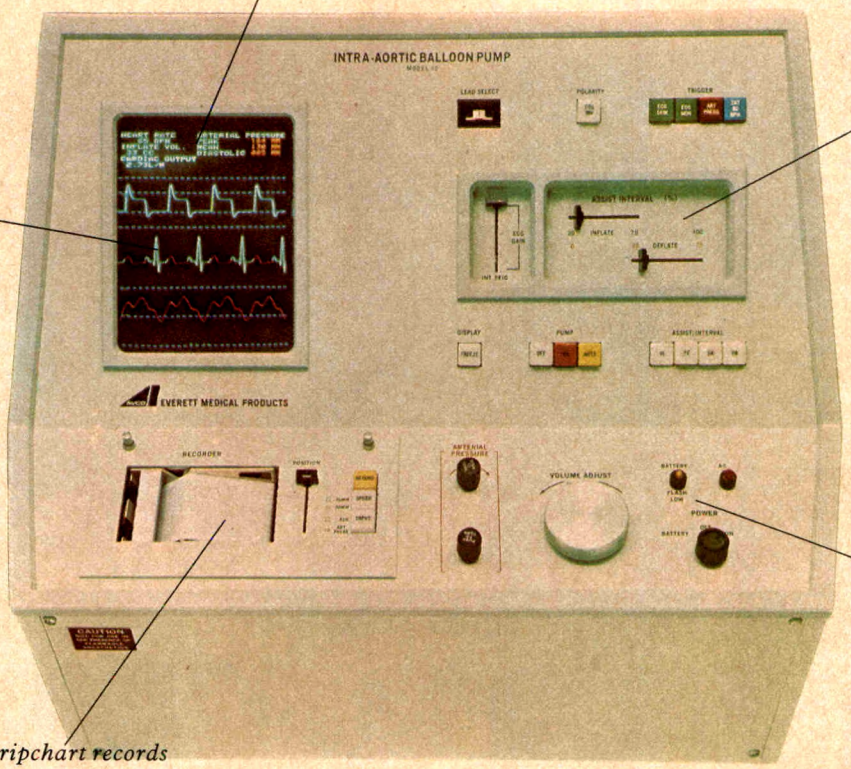
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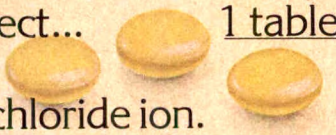
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■ Well accepted by patients–may make a significant contribution to better patient management because it is a tablet.

■ Convenient–can be taken any time, any place, as you direct... 1 tablet t.i.d. provides 20 mEq each of potassium and chloride ion.

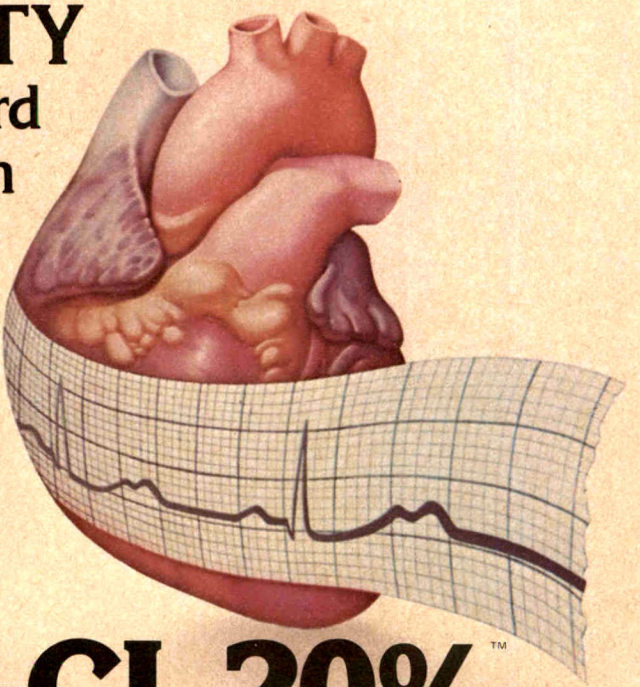


■ Clinically Effective–provides bioavailability of potassium equal to liquids. The unique waxy-matrix minimizes the likelihood of high localized concentrations of potassium near the bowel wall. Frequency of small bowel lesions is much less with wax-matrix tablets (1 per 100,000 patient years) than with enteric-coated tablets (40-50 per 100,000 patient years) but a few cases have been reported.

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A special hazard for the patient on a diuretic* or diuretic*-digitalis regimen.



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...THE PRACTICAL THERAPEUTIC

■ Once-a-day–one tablespoon (15 ml) provides a daily dosage of 40 mEq of potassium...and can be administered in dosages up to 120 mEq daily, if needed.

■ Economical–one of the least costly forms of KCl supplementation, on a mEq basis, that you can prescribe.

■ Well-tolerated—a pleasant cherry flavor mixes well in water or other liquids. KAON-CL 20% must be diluted before administration to avoid gastrointestinal irritation.



■ Therapeutically valuable in treating hypokalemia or mild digitalis intoxication. Potassium supplements should not be administered with potassium-sparing diuretics such as spironolactone and triamterene.

PLEASE SEE FOLLOWING PAGE FOR BRIEF SUMMARY OF PRESCRIBING INFORMATION.

*Thiazides, furosemide and ethacrynic acid.

WARREN-TEED
PHARMACEUTICALS INCORPORATED
SUBSIDIARY OF ROHM AND HAAS COMPANY
COLUMBUS, OHIO 43215

Kaon-CL Tabs® (potassium chloride) Controlled Release Tablets

Description: Kaon-CL Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg. potassium chloride (equivalent to 6.67 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: Kaon-CL Tabs is indicated for the treatment of potassium depletion in patients with hypokalemia and metabolic alkalosis, and for the treatment of digitalis intoxication. During therapy serum potassium levels should be monitored and the dosage titrated to achieve the desired clinical and laboratory effects. Kaon-CL Tabs is also indicated for the prevention of potassium depletion when the dietary intake of potassium is inadequate for this purpose. The prophylactic administration of potassium ion may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure, hepatic cirrhosis with ascites, patients with hypertension on long-term diuretic therapy, hyperaldosteronism states with normal renal function, the nephrotic syndrome, and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

Warnings: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-CL Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric coated potassium chloride tablets (40-50 per 100,000 patient-years), a few cases associated with wax-matrix tablets have been reported. These data are from foreign marketing experience. Kaon-CL Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

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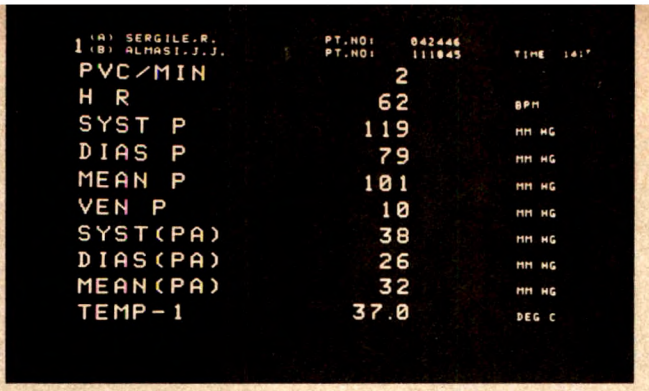
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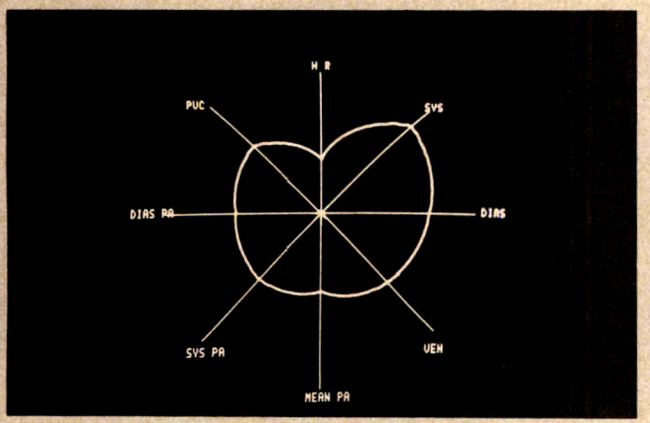
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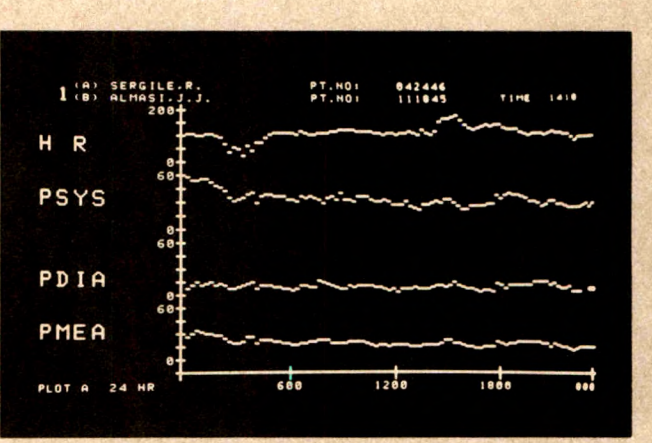
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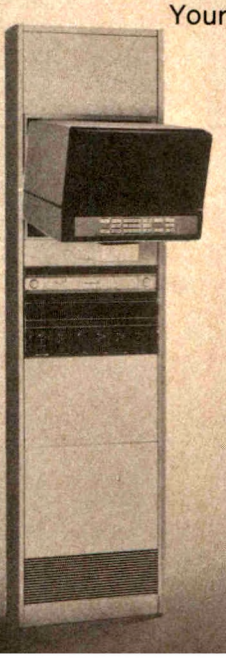
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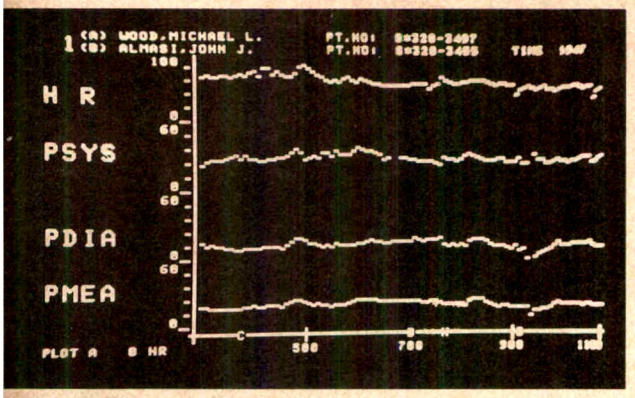


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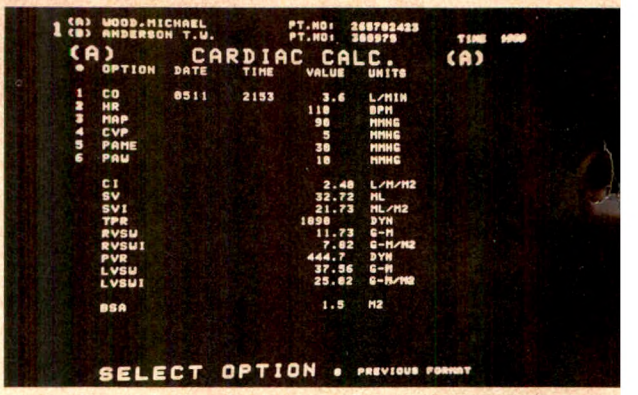
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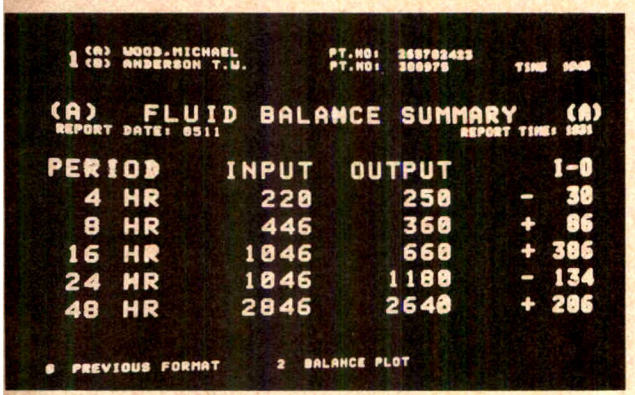


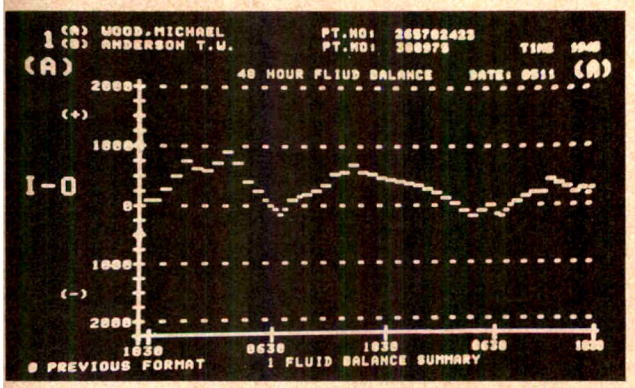
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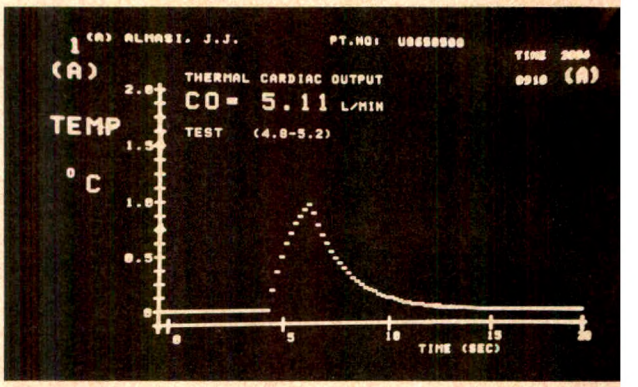


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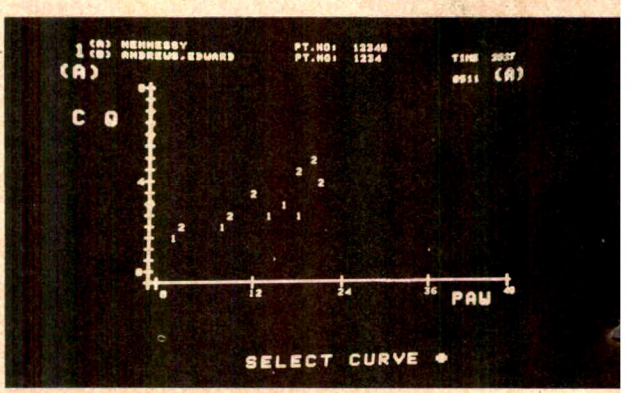






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Double Outlet Left Ventricle

Morphology, Cineangiocardiographic Diagnosis and Surgical Treatment

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BRIAN G. BARRATT-BOYES, MB, ChM, FRACS
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Auckland, New Zealand

In double outlet left ventricle, both the pulmonary artery and the aorta arise from the morphologic left ventricle. This paper presents the anatomic and cineangiocardiographic features of five patients who had this condition proved at surgery or autopsy. The condition of the first patient was incorrectly diagnosed as transposition of the great arteries with pulmonary stenosis and ventricular septal defect; the anatomic features were correctly interpreted at operation in 1966 and appropriate repair was made, but the patient died postoperatively. The condition of the other four patients was correctly diagnosed. The second patient had Ebstein's malformation of the tricuspid valve and hypoplastic right ventricle in addition to double outlet left ventricle; her condition was not considered operable. Two patients, one with visceroatrial situs solitus, concordant *d*-loop and dextrocardia, were surgically treated with good long-term results. The fifth patient died 2 years postoperatively and is the first patient reported to have double outlet left ventricle with visceroatrial situs inversus, a discordant *d*-loop and levocardia.

The segmental approach to the classification and diagnosis of connection disorders is discussed and the radiologic criteria by which double outlet left ventricle may be diagnosed considered in detail. The importance of using the radiologic projection (usually left anterior oblique) that profiles the ventricular septum is emphasized because the diagnosis can be established only by delineating the relations of the origins of the great arteries to the ventricular septum. The surgical significance of other anatomic features, including the number, size and position of ventricular septal defects and conal malformations, is also discussed.

Double outlet left ventricle is a congenital cardiac malformation in which both the aorta and the pulmonary artery arise from the morphologic left ventricle. This uncommon type of ventriculoarterial relation was first described comparatively recently.[1,2] With subsequent reports,[3–9] we have become aware of a total of eight fully documented cases and of four further cases incompletely documented or unconfirmed at surgery or necropsy.

This paper presents the experience in our institution with five cases of double outlet left ventricle, defining the anatomic types encountered and correlating the radiologic findings with the anatomic features observed at surgery or autopsy. The radiologic diagnostic features of double outlet left ventricle and their differentiation from findings in other types of ventriculoarterial relations are discussed.

Case Material and Clinical Course

Five patients with a confirmed diagnosis of double outlet left ventricle were encountered between 1966 and 1972. All five patients had had cyanosis or a heart murmur or both, as newborns. The clinical data and chest X-ray appearance on admission to this hospital are summarized in Table I, and the chest roentgenograms of Cases 3 and 5 are illustrated (Fig. 1).

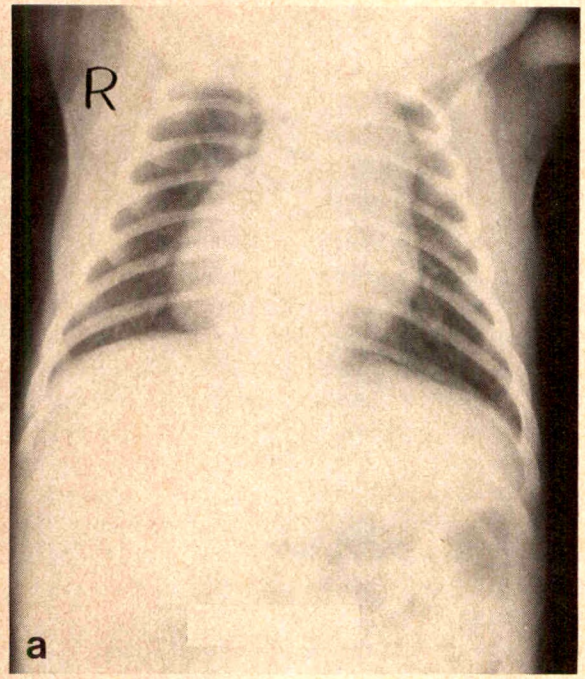
From the Green Lane Hospital, Auckland, New Zealand. Manuscript received November 20, 1975; revised manuscript received March 15, 1976, accepted March 18, 1976.

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Cardiac catheterization studies were performed at age 3 days to 26 years. Arterial desaturation (43 to 84 percent) was measured in four patients. Systolic pressures in the right and left ventricles and the aorta were equal. Gradients of 22 and 45 mm Hg, respectively, between the left ventricle and pulmonary artery were recorded in Cases 1 and 2. The pulmonary artery was not entered in the other cases.

The anatomic features were demonstrated with angiocardiography and cineangiocardiography: The preoperative diagnosis in Case 1 after angiocardiography at age 2 months and cineangiocardiography at age 3 years was transposition of the great arteries with ventricular septal defect and pulmonary stenosis (Fig. 2). The correct diagnosis was established at operation and autopsy. In the remaining patients the



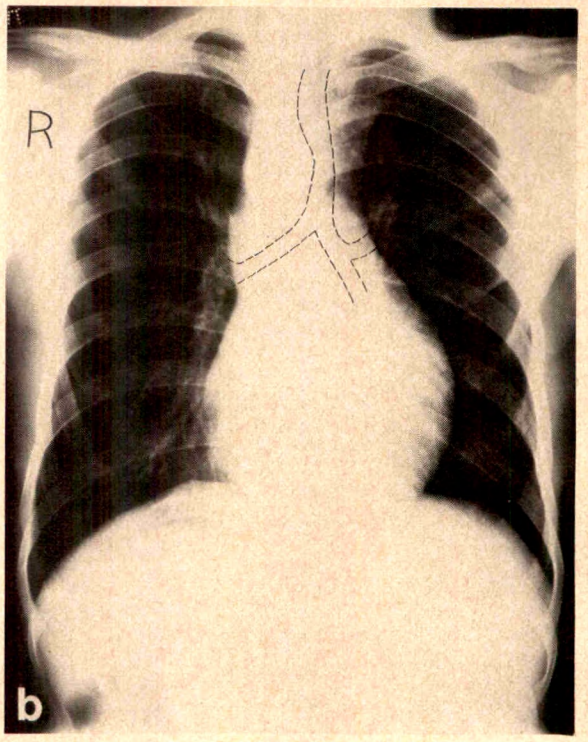


FIGURE 1. Chest roentgenograms. **a,** Case 3. Supine view at age 1 day showing visceral situs solitus with liver shadow on the right, stomach and aortic arch on the left. There is dextrocardia. Lung vascularity is normal or oligemic. **b,** Case 5. Erect frontal view showing visceral situs inversus with liver on the left, stomach and aortic arch on the right, right bronchus on the left, left bronchus on the right. There is levocardia. Lung vascularity is normal or oligemic.

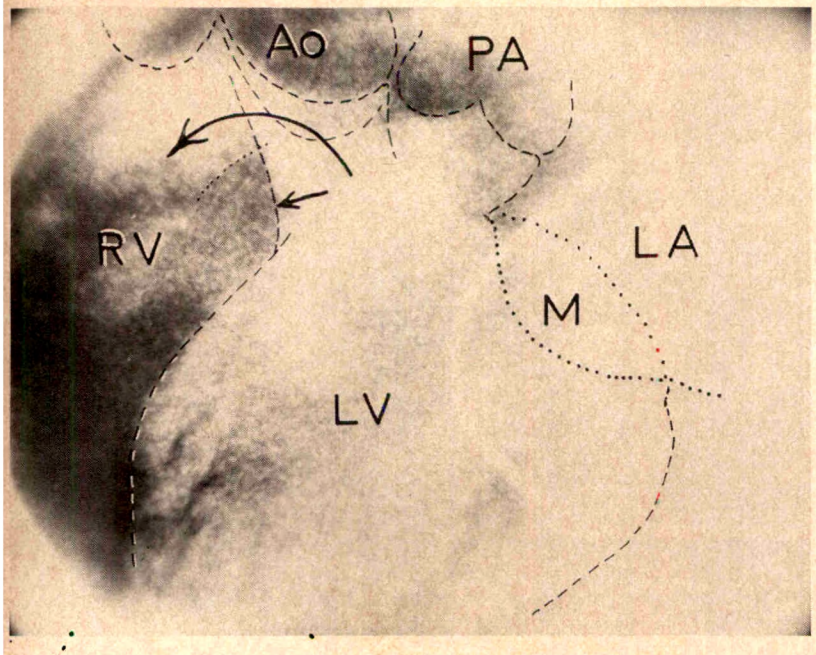


FIGURE 2. Case 1. Left ventricular cineangiocardiogram, lateral projection at age 3 years, 5 months. The posteriorly placed pulmonary artery (PA) arises from a short outflow tract close to the mitral valve (M). The aortic valve (Ao) lies anteriorly, two aortic sinuses lying behind the interventricular septum **(small arrow)** and therefore in the left ventricle (LV), the third overriding the right ventricle (RV). Flow **(large arrow)** through the ventricular septal defect to the right ventricle shows that the defect is high, though not well profiled in the lateral view. LA = left atrium.

TABLE I

Clinical Findings

Case no.	Sex, Age	Cyanosis	CHF	Auscultation: Systolic Murmur	Auscultation: Second Sound	ECG: Axis	ECG: VH	Chest Roentgenogram: Visceral Situs	Chest Roentgenogram: Aortic Arch	Chest Roentgenogram: Cardiac Position	Chest Roentgenogram: CTR (%)	Chest Roentgenogram: Pulmonary Vascularity	Clinical Diagnosis
1	M, 2 mo	+	—	Ej.	Split	+90 CW	CVH	Solitus	Left	Left	56	Plethoric	TGA ± VSD
2	F, 4 mo	±	+	Pan.	Single	−20 CCW	CVH	Solitus	Left	Left	68	Plethoric	VSD + ?PDA
3	F, 1 day	++	—	Ej.	Split	+120 CCW	—	Solitus	Left	Right	45	Normal to oligemic	Tri. atresia, VSD, small RV
4	M, 3 days	±	—	Pan.	Split	+90 CW	—	Solitus	Left	Left	54	Normal	L-R shunt
5	M, 26 yr	++	—	Pan.	Single	CHB		Inversus	Right	Left	47	Normal to oligemic	/-TGA + PS

CCW = counterclockwise; CHB = complete heart block; CHF = congestive heart failure; CTR = cardiothoracic ratio; CVH = combined ventricular hypertrophy; CW = clockwise; ECG = electrocardiogram; Ej. = ejection; / = levo; L-R = left to right; Pan. = pansystolic; PDA = patent ductus arteriosus; PS = pulmonary stenosis; RV = right ventricle; TGA = transposition of great arteries; Tri = tricuspid; VH = ventricular hypertrophy; VSD = ventricular septal defect. + = mild; ++ = moderate; ± = intermittent.

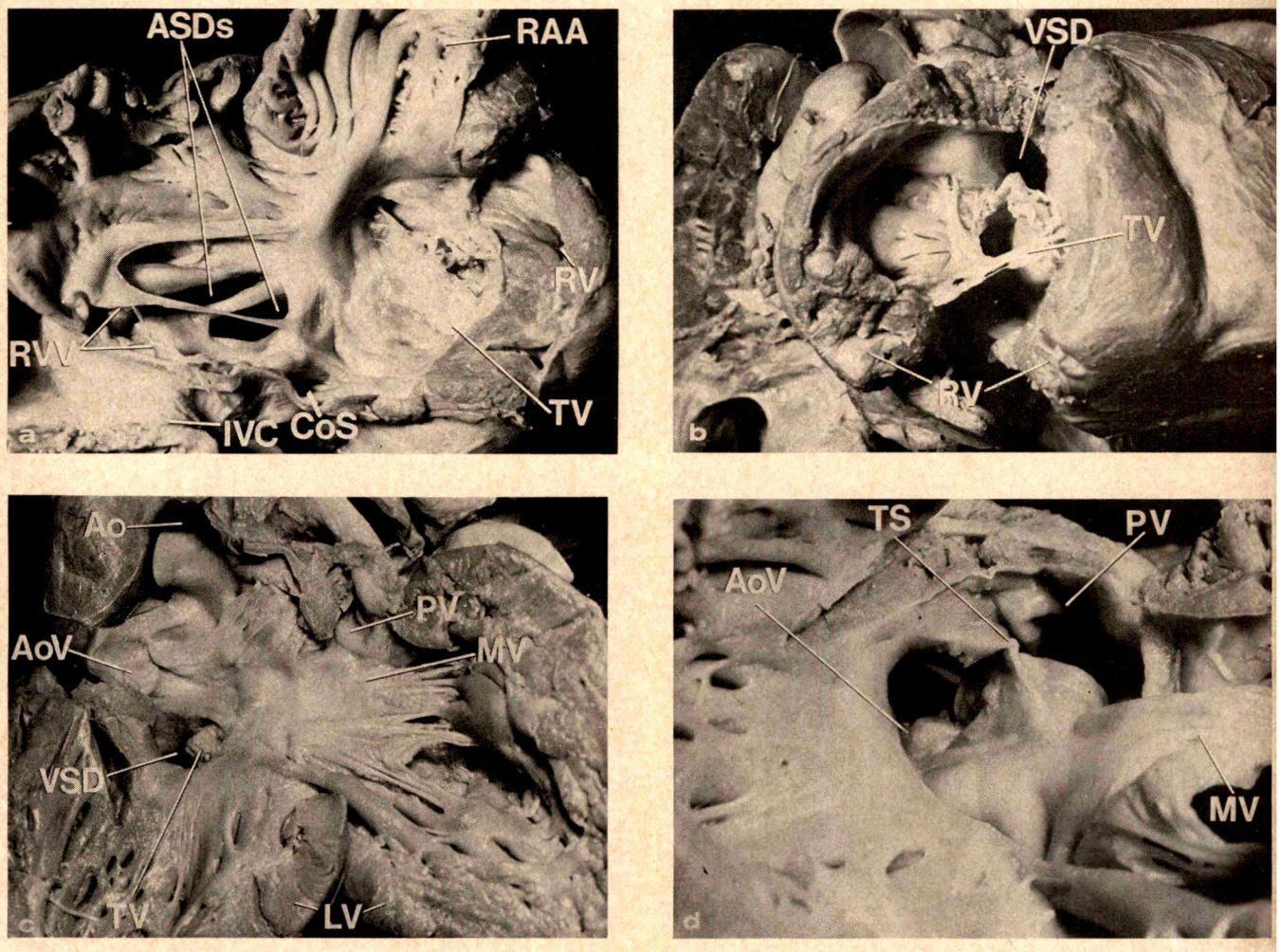


FIGURE 3. Case 2. Heart specimen. **a,** opened right atrium, tricuspid valve (TV) and right ventricular (RV) inflow. Secundum atrial septal defects (ASDs) were due to deficiency and fenestration of the septum primum. The septal leaflet of the tricuspid valve was abnormally adherent to the ventricular septum and the anterior leaflet was elongated. CoS = coronary sinus; IVC = inferior vena cava; RAA = right atrial appendage; RVV = right venous valve remnants. **b,** hypoplastic right ventricle viewed from the apex looking toward the ventricular septal defect (VSD), which is the only outlet. **c,** left ventricular (LV) outflow to opened, bicuspid aortic valve (AoV) and pulmonary valve (PV). The ventricular septal defect is separated by 4 mm from the aortic valve. The tricuspid valve is visible through the defect. Note the pulmonary to mitral valve (MV) and aortic valve to mitral valve fibrous continuity. **d,** closeup view of left ventricular outflow showing aortic to mitral and pulmonary to mitral fibrous continuity. The aortic and pulmonary valves are separated by a thin fibrous ridge that has been called the truncal septum (TS).[2]

cineangiocardiographic diagnosis of double outlet left ventricle was confirmed either at autopsy (Case 2, Fig. 3) or at operation (Cases 3, 4 and 5, Fig. 4 to 6).

The surgical procedures and follow-up data in Cases 1, 3, 4 and 5 are summarized in Table II. Patient 1 died at the end of operation; although autopsy was performed, the heart specimen has been lost. Patient 5 died elsewhere 2 years postoperatively. Complete heart block, present preoperatively, was the presumed cause of death, but no autopsy was performed.

Patient 2 was not considered to have an operable condition. She died at age 21 weeks with respiratory problems and congestive heart failure.

Anatomic Findings

The anatomic findings are summarized in Figure 7.

Cases 1 to 4 had situs solitus of viscera and atria and concordant ventricular *d*-loops. Case 5 had situs inversus and a discordant *d*-loop (Fig. 1b and 6b). There was hypoplasia of

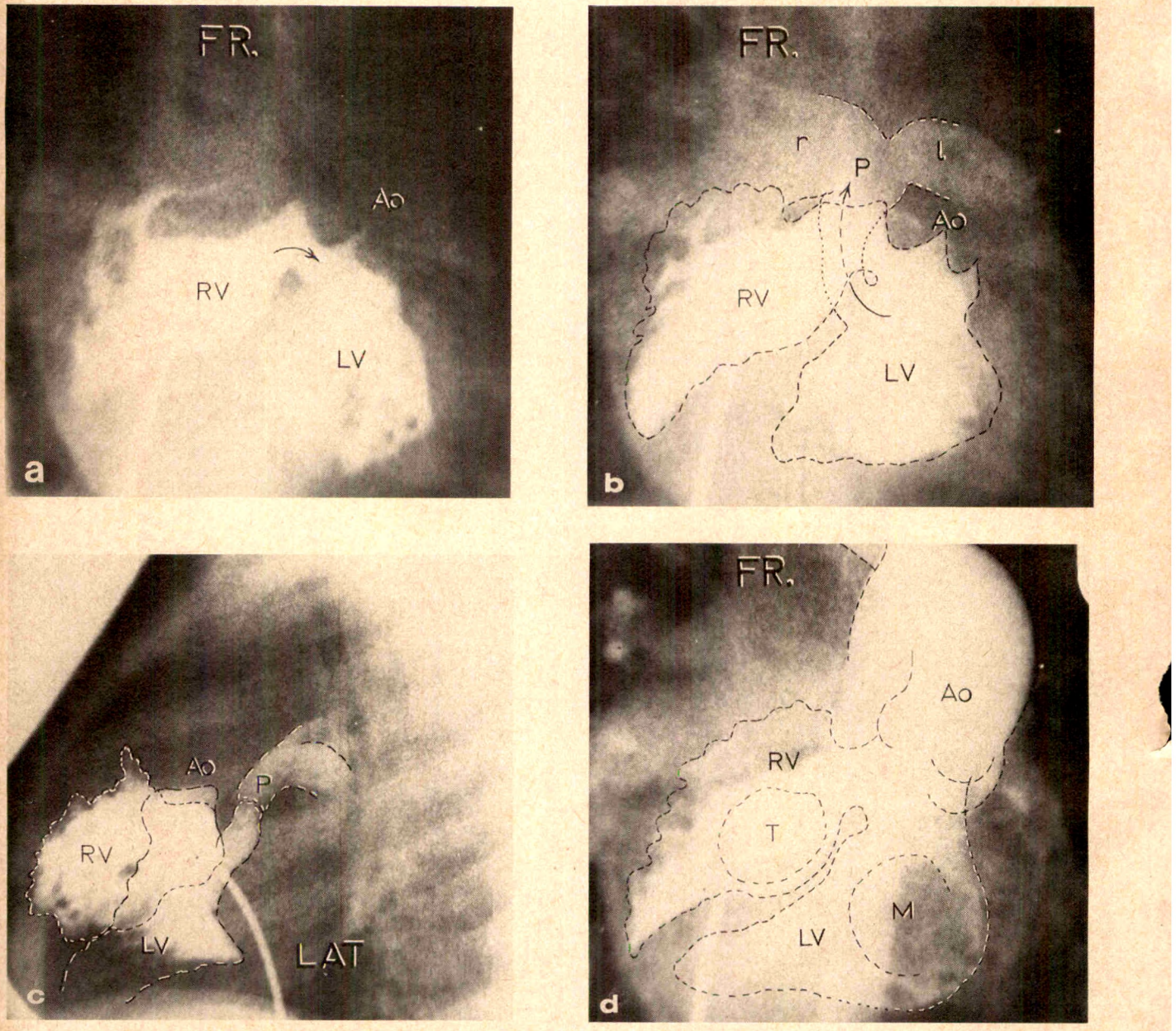


FIGURE 4. Case 3 (with dextrocardia). Frames from biplane frontal (FR.) and lateral (LAT) right ventricular cineangiocardiogram. **a,** ectopic systole early in the run. Contrast medium flows from the right ventricle (RV) through a subaortic ventricular septal defect **(arrow)** to the left ventricle (LV) outlining the closed aortic leaflets, but does not enter the aorta (Ao). **b** and **c,** later in the same ectopic systole. The left ventricle is more completely filled and contrast medium flows through the long narrow outflow tract **(arrow)** lying posteriorly and to the right of the aorta to fill the pulmonary artery (P) and its right (r) and left (l) branches. Doming of the pulmonary valve is visible, and the pulmonary valve ring and proximal main pulmonary artery are also narrowed. The aortic valve is still closed. The pulmonary outflow and the aortic valve both arise entirely from the left ventricle. **d,** later in the run. Diastolic frame shows the tricuspid (T) and mitral (M) valves. The ventricular septum is well profiled in the frontal projection, the cardiac apex directed toward the right. The morphologic right ventricle with typical coarse trabeculations lies rightward and above the left ventricle. The aorta is left of the pulmonary artery. The lateral view (not illustrated) showed it also to lie anteriorly.

the right ventricle and an Ebstein-like malformation of the tricuspid valve in Case 2 (Fig. 3, a and b).

A subaortic ventricular septal defect was present in all five patients (Fig. 2; 3c; 4a; 5, a and b; and 6, a and b). Aortic overriding was present in Cases 1, 4 and 5 (Fig. 2; 5, a and b; and 6b).

The conal anatomy in Case 1 is not clear. The subaortic and subpulmonary free wall and septal conal musculature was deficient in Case 2 (Fig. 3, c and d). A poorly developed subpulmonary conus in Cases 3 and 4 appeared to cause subpulmonary stenosis (Fig. 4, b and c; and 5, b to d), and the cineangiocardiographic relations were consistent with absent subaortic conus (Fig. 4d; and 5, a, c and d). In Case 5 bilateral free wall conal deficiency with a small conal septum that

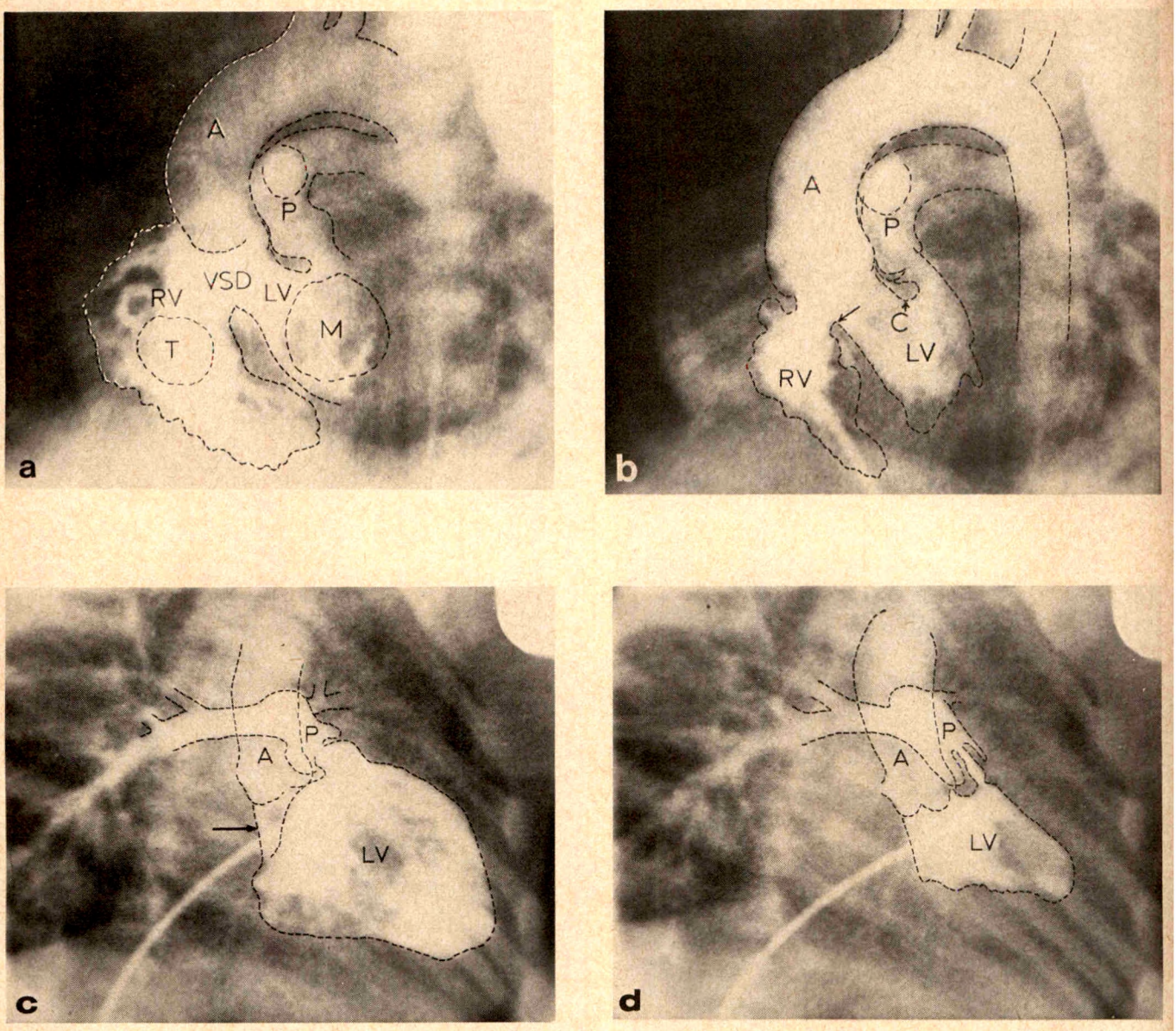


FIGURE 5. Case 4 (normally positioned heart). Frames from biplane right and left ventricular cineangiocardiograms in oblique projections. **a,** diastolic frame during right ventricular injection, left anterior oblique view. Contrast medium flows from the typically coarsely trabeculated morphologic right ventricle (RV) through the ventricular septal defect (VSD) into the left ventricle (LV). There has already been some filling of the aorta (A) and pulmonary artery (P), which are well separated, consistent with a rightward anterior aortic position relative to the pulmonary artery. Nonopaque flow reveals the tricuspid (T) and mitral (M) valves opening normally into the right and left ventricles. The basal septum between the atrioventricular valves is intact, the ventricular septal defect lying above them. The distance between the aortic and mitral valves in this projection is within the normal range, consistent with aortic-mitral fibrous continuity. **b,** systolic frame slightly later in right ventricular cine study confirms the subaortic location of the ventricular septal defect, the upper margin of the basal septum, that is, the lower margin of the defect **(larger arrow),** indicating that the aorta arises from the left ventricle except for the rightward anterior sinus, which arises from the right ventricular free wall. The conal septum (C) is entirely within the left ventricle. The leftward posterior aspect of the subpulmonary conus arises from the left ventricular free wall above the mitral valve. **c,** diastolic frame in right anterior oblique projection during left ventricular injection (catheter through ventricular septal defect). The low position of the aortic root, showing normal relation to the atrioventricular septum **(arrow),** suggests normal deficiency of the subaortic conus. Overlap of the aorta and the pulmonary artery indicates (by correlating with the left anterior oblique view in **a** and **b**) that the aorta is rightward and slightly anterior to the pulmonary artery. The subpulmonary conus shows only slight restriction in diastole. **d,** systolic frame shortly after **c.** There is marked narrowing of the subpulmonary conus indicating its muscular and obstructive nature.

contributed to subpulmonary stenosis was shown (Fig. 6, b to d). This conal septum was found at operation to consist of a fibromuscular ridge, which was excised.

All five patients had pulmonary stenosis. Three had a bicuspid pulmonary valve. The pulmonary valve rings were small in three patients. In Cases 1 and 5 supravalvular narrowing contributed to the pulmonary stenosis. Subpulmonary obstruction was produced by a poorly developed subpulmonary conus in Cases 3 and 4 and a fibromuscular ridge and redundant valve-like tissue in Case 5.

The great arterial interrelations were *d*-malposition in four cases (Fig. 7). The exception (Case 3) had *l*-malposition with isolated dextrocardia and unusual ventricular positions.

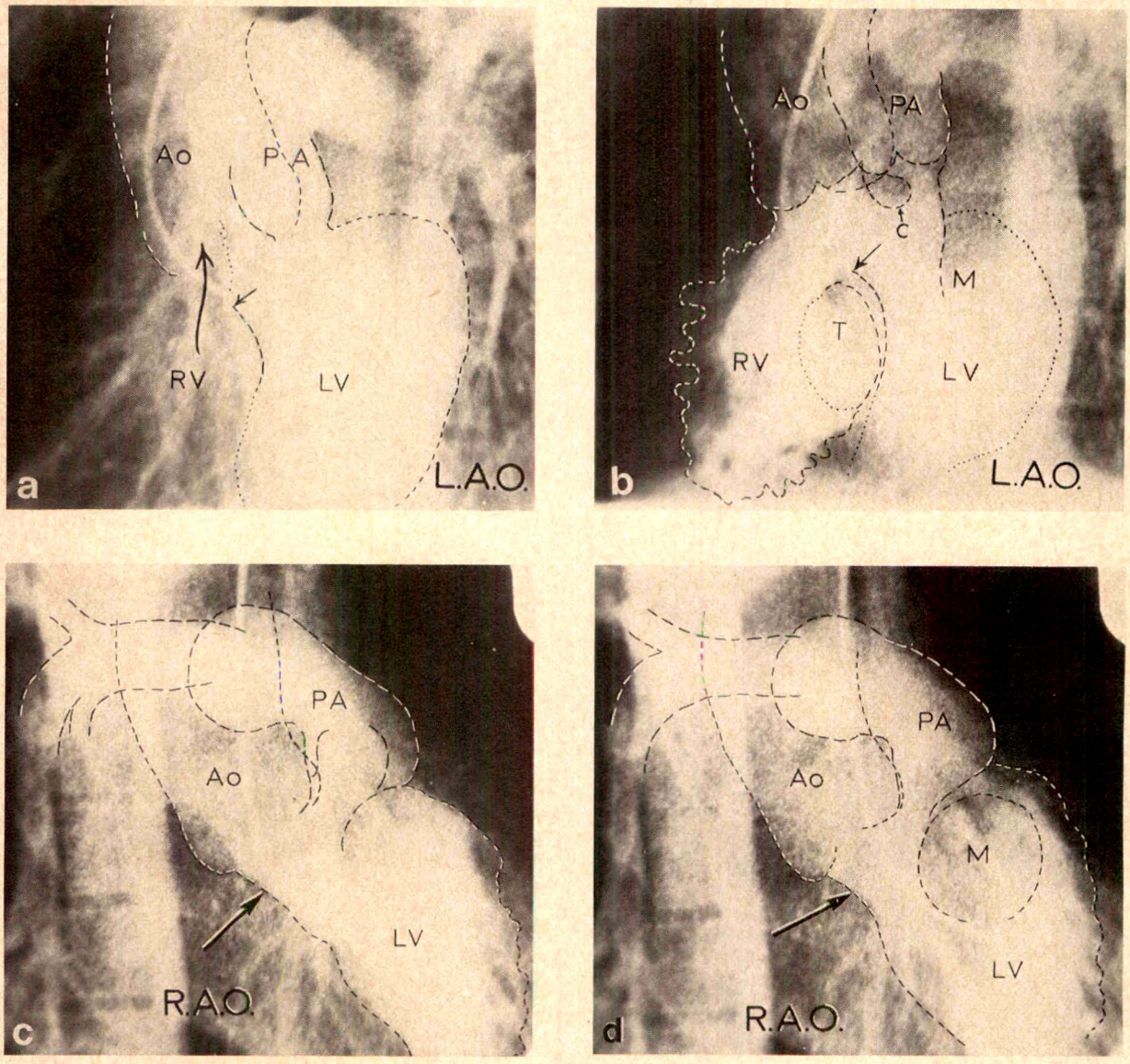


FIGURE 6. Case 5. Frames from single plane left and right ventricular cineangiocardiograms. **a,** systolic frame in the left anterior oblique (L.A.O.) view during left ventricular injection. The finely trabeculated morphologic left ventricle (LV) ejects contrast medium to the pulmonary artery (PA) and aorta (Ao) which overlap, consistent with a side by side relation, with the aorta to the right (correlate **c** and **d**). Nonopaque flow **(large arrow)** through the subaortic ventricular septal defect dilutes contrast medium in the aorta. The basal septum is outlined up to the lower margin of the ventricular septal defect **(small arrow).** RV = morphologic right ventricle. **b,** diastolic frame in the left anterior oblique (L.A.O.) projection during right ventricular injection. The coarsely trabeculated morphologic right ventricle lying rightward and anteriorly (*d*-loop) receives the right-sided atrioventricular valve, presumably the tricuspid valve (T), seen with nonopaque flow. The ventricular septum is well profiled. Contrast medium has also partly filled the left ventricle receiving the left-sided atrioventricular valve, presumably the mitral valve (M). The conal septum (c) is entirely in the left ventricle, separating the pulmonary from the aortic outflow. Proximity of the pulmonary valve to the mitral valve, the left ventricular origin of the pulmonary outflow and mainly left ventricular origin of the aorta are shown. The rightward anterior aortic sinus rides through the ventricular septal defect **(lower margin, arrow)** and arises from the right ventricular free wall. **c.** systolic and **d,** diastolic frames in the right anterior oblique (R.A.O.) view after left ventricular injection. The low position of the aortic valve, its normal relation to the atrioventricular septum **(arrows)** and proximity to the mitral valve (M) suggest normal deficiency of subaortic conus. Subvalvular pulmonary outflow obstruction and systolic doming of the pulmonary valve (bicuspid at operation) are also present. The aortic and pulmonary valve rings slightly overlap (correlate with **a** and **b**), consistent with a side by side relation.

The coronary arterial origins and distribution are shown diagrammatically in Figure 7. In Case 1 they were similar to the common pattern seen in patients with *d*-transposition, the noncoronary sinus lying anteriorly and the left anterior descending and left circumflex arteries passing in front of the pulmonary artery.[10] A single left coronary artery was present in Case 2. In Case 3 the coronary arteries arose from an anterior sinus. In Case 4 the right coronary artery arose anteriorly and gave origin to the anterior descending artery; the left circumflex artery arose posteriorly, passing behind the pulmonary artery. The coronary arteries were not clearly demonstrated in Case 5.

Discussion

The surgical treatment of complex congenital cardiac lesions necessitates complete and accurate preoperative assessment so that the most appropriate operation can be planned. The need for a clear understanding of the proximal to distal relations (the connections) of the heart chambers and great vessels has stimulated reappraisal of the classification of congenital heart disease.[11] The segmental approach to diagnosis[12] is of great value in clarifying these important relations and has itself indicated a need to return to a literal definition of transposition and other anomalies of the conotruncal region.[13] The recognition of certain spatial relations of the great arteries at semilunar valve level gives a useful diagnostic clue, but does not guarantee any particular ventriculoarterial connection: transposition of the great arteries, double outlet right ventricle, double outlet left ventricle, anatomically corrected malposition or normally arising great arteries.[14] The anatomic types of conus encountered are also variable[15] and should therefore not be used as definitive criteria in the formulation of definitions of these ventriculoarterial connections.

TABLE II

Surgical Procedures and Results in Four Cases

Case no.	Age and Date of Surgery	Repair	Results
1	3 yr, 6 mo (Nov. 7, 1966)	Closure VSD, leaving Ao in LV; Closure PA; Ao homograft conduit RV – PA	Hospital death
3	2 yr, 10 mo (Feb. 13, 1973)	Closure VSD, leaving Ao in LV; Closure PA; Ao homograft conduit RV – PA; Closure ASD	2 1/2 yr postop, well
4	1 yr, 6 mo (Mar. 26, 1973)	Closure VSD, leaving Ao in LV; Closure PA; Ao homograft conduit RV – PA; Closure ASD	2 1/2 yr postop, well
5	26 yr (Aug. 16, 1972)	Closure VSD connecting Ao to RV; (discordant ventricular loop); direct relief PS	Late death, 2 yr postop

Ao = aorta; ASD = atrial septal defect; LV = left ventricle; PA = pulmonary artery; postop = postoperative; PS = pulmonary stenosis; RV = right ventricle; VSD = ventricular septal defect.

Diagnostic Criteria

Only consideration of internal relations allows the confident diagnosis of double outlet left ventricle to be made; that is, the relation of the aorta or pulmonary artery to the ventricular septum determines the site of origin of the great artery. As suggested by Van Praagh,[14] it is helpful to make two types of diagnosis, the arterioventricular relation and the conotruncal malformation. We suggest that a complete diagnosis should indicate (1) the segmental combination that defines the proximal to distal relations or *connections* in the heart; (2) the *malformations* encountered in relation to each segment; and (3) *unusual spatial positions* of heart, cardiac chambers or great arteries. In considering co-

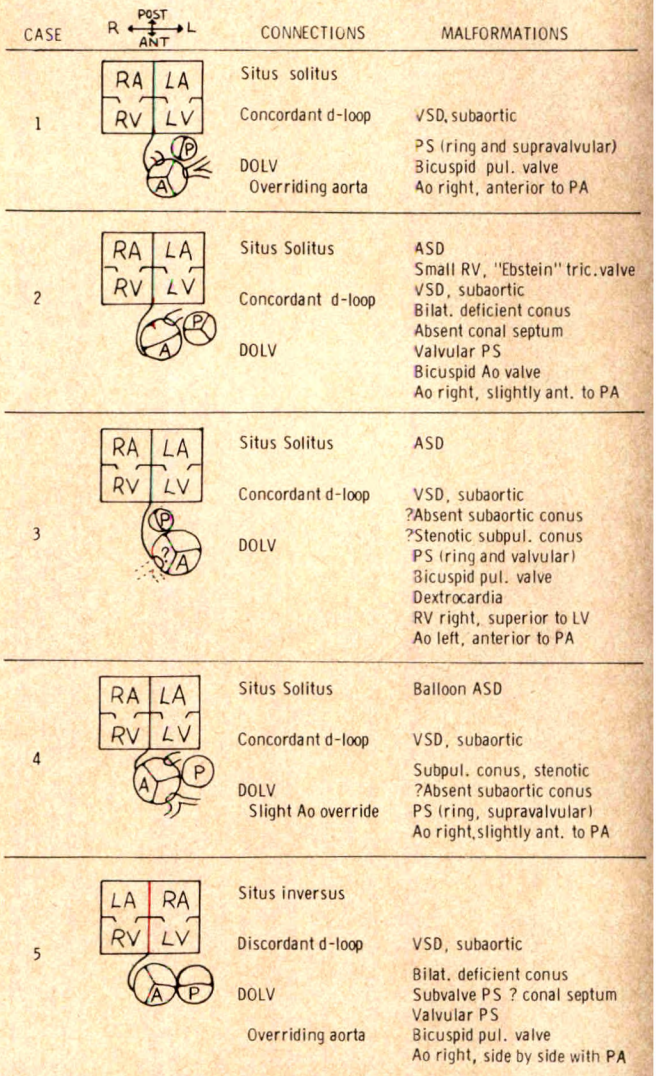


FIGURE 7. Anatomic findings. On the left are plan views of cardiac chamber and great arterial connections. The coronary arterial origins are indicated where known (see text). A = aortic valve; ANT, ant. = anterior; Ao = aorta; ASD = atrial septal defect; Bilat. = bilateral; d = dextro; DOLV = double outlet left ventricle; L = left; LA = left atrium; LV = left ventricle; P = pulmonary valve; PA = pulmonary artery; POST = posterior; PS = pulmonary stenosis; pul. = pulmonary; R = right; RA = right atrium; RV = right ventricle; Subpul. = subpulmonary; tric. = tricuspid; VSD = ventricular septal defect.

notruncal anomalies, the "connections diagnosis" indicates which great artery arises from which ventricle and does not presume any particular type of conal anatomy. The conal anatomy is described with the malformations that may be present.

If there is no ventricular septal defect,[2] then the diagnosis of double outlet left ventricle can readily be established by angiocardiography in each ventricle. Usually there is a ventricular septal defect and one of the great arteries arises near it. To determine the ventricular origin of either great artery, one must study in detail its relations to the ventricular septum and the boundaries of the ventricular septal defect as well as the free wall ventricular attachments of the semilunar valve ring or its outflow tract. Apart from the diagnostic relations mentioned, the size, shape, number and position of defects in the septum, the relation of the atrioventricular valves to the septum, the anatomy of the subaortic and subpulmonary outflow tracts and the position and size of the conal septum must be evaluated so that the most appropriate surgical correction can be planned.

Radiologic Technique

Complex congenital heart disease is best diagnosed using biplane cineangiocardiography. A complete three-dimensional appreciation of the anatomy of each case is essential and requires a flexible approach. Selection of both injection sites and projections depends upon the individual problem.

The variable clinical diagnosis in our patients with double outlet left ventricle influenced the initial choice of injection site and projection for cineangiocardiography. To clarify the diagnosis, injections in both ventricles may be necessary. Although left ventricular injections have been preferred in double outlet left ventricle,[3,4,8] in our experience a right ventricular cineangiocardiogram can be as diagnostic if the septum is profiled (Fig. 4; 5, a and b; and 6b). When the heart and ventricles are in normal position the sinus septum is usually well profiled in the left anterior oblique projection (Fig. 5, a and b). We commonly use biplane oblique views for this reason. However, when the heart is in an unusual position the septum may best be profiled in another view such as the frontal view (Fig. 4, a, b and d).

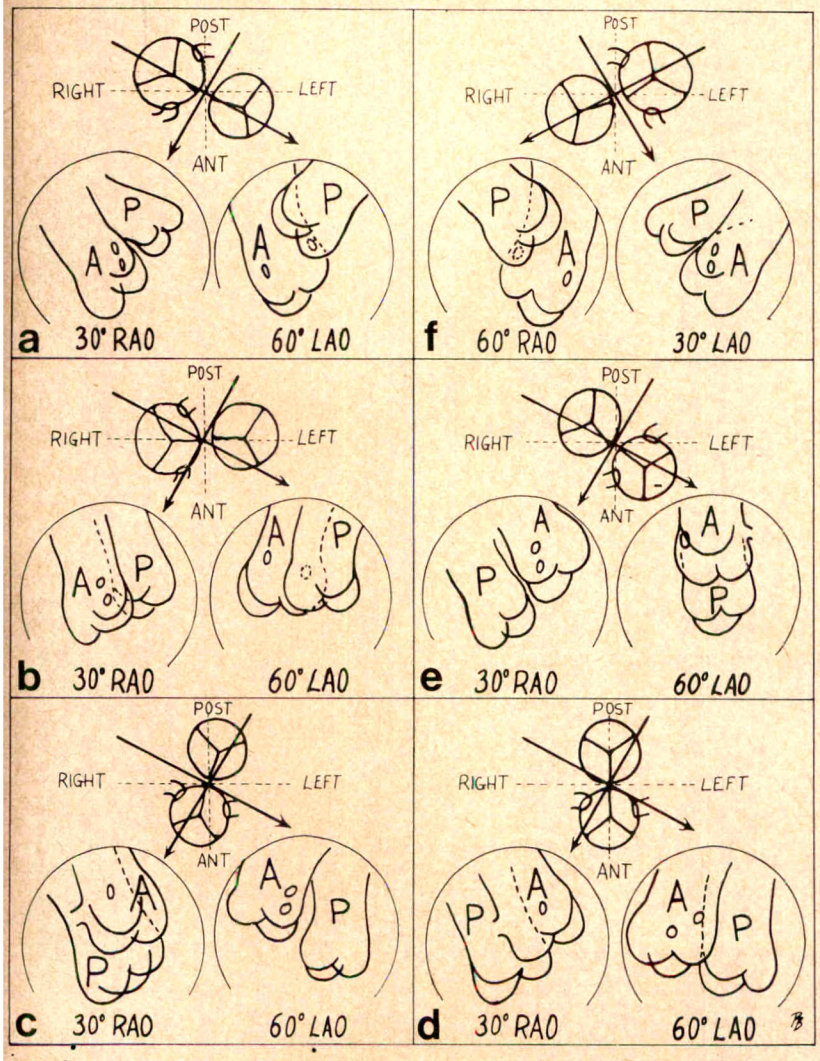


FIGURE 8. The relative positions of the aorta (A) and pulmonary artery (P) as viewed in perpendicular right anterior oblique (RAO) and left anterior oblique (LAO) projections are shown for the relations illustrated in the accompanying horizontal body cross-sectional diagrams. The valves have been drawn with vertical relations and orientation suggesting the most usual conal anatomy and ventriculo-arterial connection expected for each of the positions: **a,** solitus normal; **b,** double outlet right ventricle; **c** and **d,** complete *d*-transposition of the great arteries; **e,** corrected *l*-transposition of the great arteries; **f,** inversus normal. The orientation and vertical relations are likely to differ in less typical cases. The plan view relations (right-left, anterior-posterior) can always be deduced from two oblique views. ANT = anterior; POST = posterior.

Assessment of the spatial relations of the origins of the great arteries is important for a complete understanding of their relations to the septum and any defects in it. Great arterial positions are readily assessed by correlating the two oblique views. Any initial difficulty experienced by those familiar with frontal and lateral views only is more than compensated for by the diagnostic advantage of profiling the septum in the left anterior oblique view. It is a good practice to draw the horizontal relation diagrams until the patterns become familiar (Fig. 8).

Left Anterior Oblique Projection

Origin of rightward or posterior great artery: In a normal heart in the usual position, the basal part of the sinus septum forming the rightward margin of the left ventricular outflow tract between the tricuspid and mitral valves is well profiled in a 45 to 60° left anterior oblique projection (Fig. 5, a and b, shows these features). This basal septum usually slopes upward from left to right, making a definite but variable angle with the more apical sinus septum which lies vertically or slopes slightly in either direction in this view. When the aorta arises normally from the left ventricle, as in a normal heart or in isolated infracristal ventricular septal defect, the whole of the aortic valve lies on the left and posterior side of the basal septum. When there is slight aortic override, similar to the situation in tetralogy of Fallot, the degree of override can be judged in relation to the upper edge of the basal septum (Fig. 5b and 6, a and b, show this feature). The overriding part of the aortic contour is often profiled, and the origin of the appropriate aortic leaflet (usually the right anterior) from the right ventricular free wall may be clearly shown. When the aorta arises from the right ventricle as in double outlet right ventricle or transposition of the great arteries, the basal septum relates most closely to the leftward posterior rim of the aortic valve if this is low in position, or to the subaortic free wall (in double outlet right ventricle) or conal septum (in transposition of the great arteries) if a well developed subaortic conus is present.

In three of our patients with double outlet left ventricle there was aortic override of some degree (Fig. 2; 5b; and 6, a and b) but only two patients were studied in the left anterior oblique projection. In another patient believed at cineangiocardiography to have double outlet left ventricle with about 50 percent override of aorta to right ventricle (Fig. 9), it was considered at surgery that two thirds of the perimeter of the aortic valve arose from the right ventricle though the whole of the left posterior sinus was on the left side of the septum. We therefore consider this case most appropriately classified as a case of transposition with overriding aorta rather than double outlet left ventricle with overriding aorta. Assessment of the degree of override is difficult in some

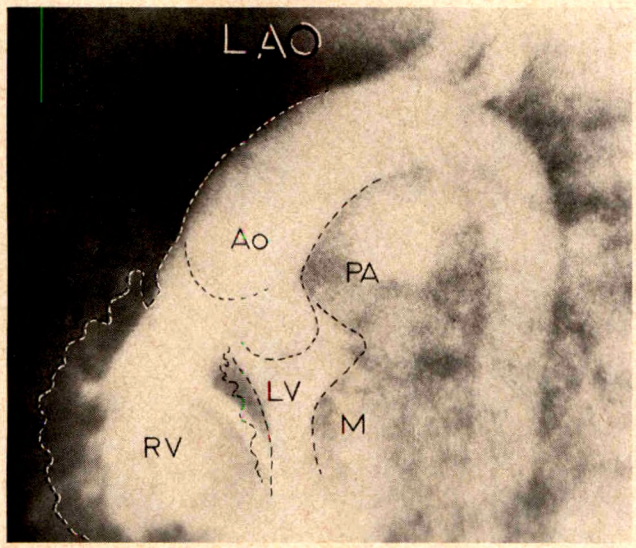


FIGURE 9. Transposition of the great arteries with overriding aorta. Diastolic cine frame (left anterior oblique [LAO] view) during injection in the right ventricle (RV). Contrast medium has filled the aorta (Ao) and the left ventricular outflow tract (LV), outlining the anterior leaflet of the mitral valve (M). The aorta overrides the basal septum. A low left posterior aortic sinus arises from the left ventricle, close to the mitral valve. A rightward sinus arises from the right ventricular free wall, and the third (anterior) sinus appears to override the septum. At operation this sinus was found in the right ventricle, hence the aortic origin is two thirds right ventricular, one third left ventricular. The pulmonary arterial (PA) origin from the left ventricle was shown early in the run and on left ventricular injection.

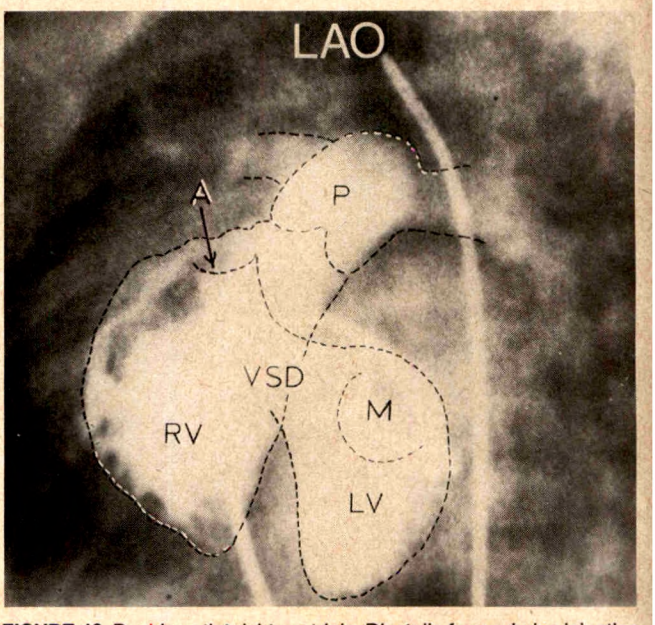


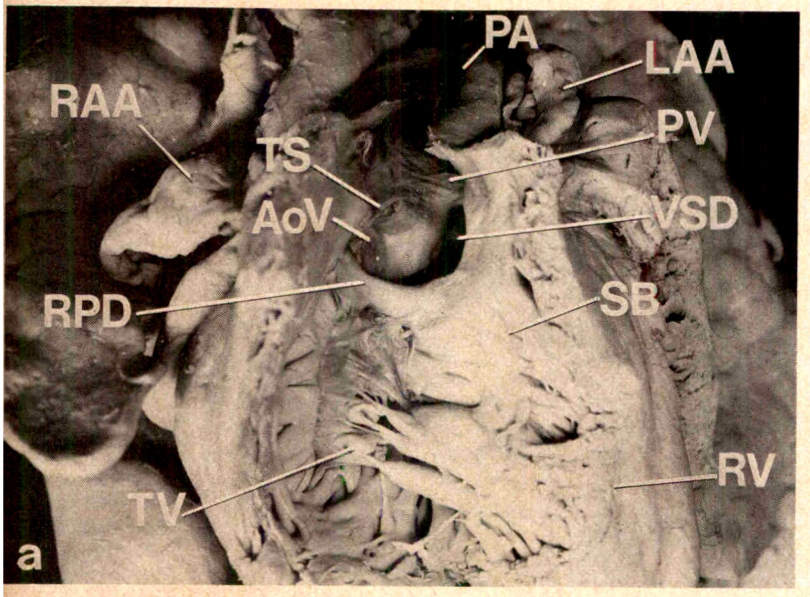
FIGURE 10. Double outlet right ventricle. Diastolic frame during injection in the left ventricle (LV) (left anterior oblique [LAO] view). The ventricular septum is well profiled and the ventricular septal defect (VSD) above the basal septum is the only outlet from the left ventricle. The pulmonary artery (P) lies in normal position above the left ventricle but is remote from the mitral valve (M), being connected to the right ventricle by a normal subpulmonary conus. The left posterior margin of the pulmonary ring takes origin from the anterior septal margin of the right ventricle (RV); the rightward anterior margin arises from the right ventricular free wall. The frame also shows the position of the aortic valve (A) in the right ventricle separated from the mitral valve by conal muscle.

cases even at autopsy and is somewhat arbitrary when the aortic valve, by overriding the septum, forms part of the boundary of the ventricular septal defect.

Origin of the leftward or anterior great artery: In a normal heart in the usual position, the right ventricular origin of the pulmonary artery in the left anterior oblique projection can be confirmed by tracing the anterior septal margin of the right ventricle to the leftward posterior margin of the pulmonary valve (as in Fig. 10). The rightward anterior margin of the pulmonary valve arises from the right ventricular free wall. Even if the left ventricle and aorta are opacified, these attachments can usually be identified with cineangiographic analysis in spite of the overlapping shadows. In double outlet right ventricle the origin of the pulmonary artery is often similar to that of the normal heart (Fig. 10). In tetralogy of Fallot the same connections can be traced, although the pulmonary valve is frequently lower in position.

In double outlet left ventricle with a normally oriented heart, the pulmonary artery is usually leftward and the pulmonary valve may appear to lie in a similar position to that of the normal heart or the heart with tetralogy of Fallot. However, its left ventricular origin remote from the basal septum is clearly indicated in the left anterior oblique projection by the leftward posterior part of the semilunar valve ring or subsemilunar conus, which arises from the left ventricular free wall (Fig. 5, a and b; and 6a).

In four of our cases the conal septum separating the pulmonary from the aortic valve was entirely in the left ventricle, and the left anterior oblique view showed this well in Cases 4 and 5 (Fig. 5, a and b; and 6b). In Case 2 the conal septum was replaced by a shallow fibrous



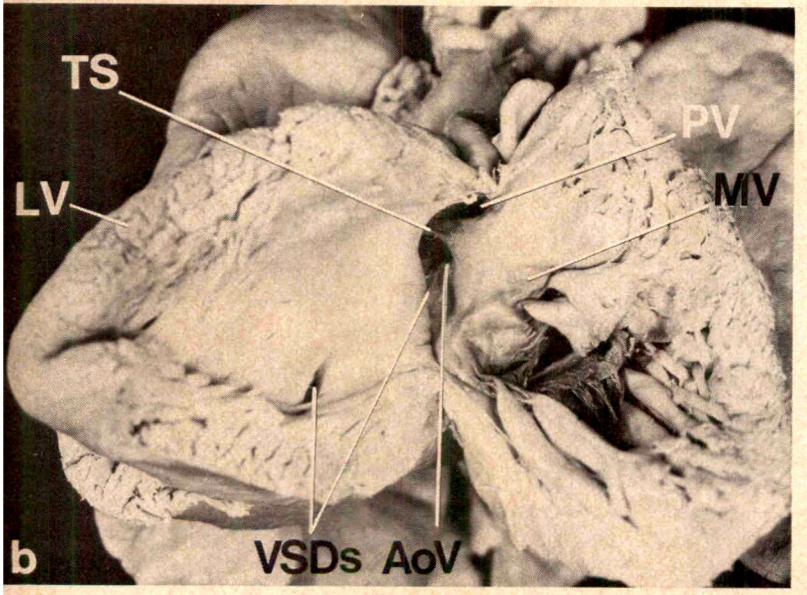


FIGURE 11. Heart specimen in double outlet both ventricles. **a,** right ventricular (RV) outflow to aortic valve (AoV) and opened pulmonary valve (PV) and pulmonary artery (PA). The truncal septum (TS) is the fibrous ridge between the semilunar valves. The conal septum is absent. The right posterior division (RPD) of the septal band (SB) separates the aortic valve from the tricuspid valve (TV). LAA = left atrial appendage; RAA = right atrial appendage. **b,** opened left ventricle (LV). There is tenuous fibrous continuity between the anterior leaflet of the mitral valve (MV) and the semilunar valves which override the ventricular septum and both ventricular cavities. In addition to the sub-semilunar defect, there is a small muscular ventricular septal defect (VSD).

ridge, and the aortic ring was contiguous with the rightward part of the pulmonary valve (Fig. 3d).

When the ventricular septal defect is anterior, relating more closely to the leftward pulmonary artery than to the rightward aorta, the pulmonary artery may override the ventricular septal defect. None of our cases of double outlet left ventricle presented this particular problem, but we have encountered it in transposition of the great arteries and in double outlet right ventricle. Difficulty in determining the degree of override can be expected, as discussed in relation to the overriding aorta.

Right Anterior Oblique Projection

In the normal heart the right anterior oblique projection profiles the atrioventricular septum, forming the rightward posterior margin of the left ventricular outflow tract.[16] The outflow septum formed by the conal septum (the leftward part of the parietal band of the crista supraventricularis) and the high anterior muscular septum are also profiled. Defects in all these areas (ventriculoatrial septal defects, atrioventricular canal defects, conal septal ["supracristal," "intracristal"] and high anterior muscular septal defects) are therefore well shown by left ventricular cineangiocardiography in this view. The sinus septum and defects within it including the most common ventricular septal defect between the two limbs of the septal band are not profiled.

In our patients with double outlet left ventricle with normally oriented ventricles, the ventricular septal defect was not profiled in the right anterior oblique view, and the most important relation of the great arteries to the septum was not directly demonstrated. However, the right anterior oblique view was an essential part of the complete evaluation for several reasons. Ventricular septal defects in unusual position could be excluded. Evaluation of interrelations of the great arteries by correlation with the left anterior oblique view was possible (Fig. 8). The positions of the great arteries in relation to the long axis of the ventricles (base to apex) were shown in ideal projection. The evaluation of the site of origin of the great arteries was aided by noting the low normal relation of the aortic valve to the atrioventricular septum and mitral valve in cases with a rightward aorta (Fig. 5, c and d; and 6, c and d). The origin of the pulmonary artery from the left ventricular free wall above the mitral valve was also apparent from left ventricular injections (Fig. 5, c and d; and 6, c and d), thus confirming the information more reliably gained from the left anterior oblique view. Evaluation of the subpulmonary conus and conal septum was also helped by these views.

Overriding of Both Great Arteries

Perhaps the greatest difficulty in assessing the origin of the great arteries, even at surgery or autopsy, is encountered when there is a large ventricular septal defect closely related to both the semilunar valve rings. The margins of the septal defect may reach from the leftward aspect of the pulmonary ring to the rightward aspect of the aortic ring. Both great arteries contribute to the upper "margin" of the defect and could be said to override to some extent (Fig. 11). Different observers under the same conditions are likely to make different diagnoses, and any observer is likely to allocate the great arteries to the ventricle through which they happen to be viewed. We have not included such cases in this re-

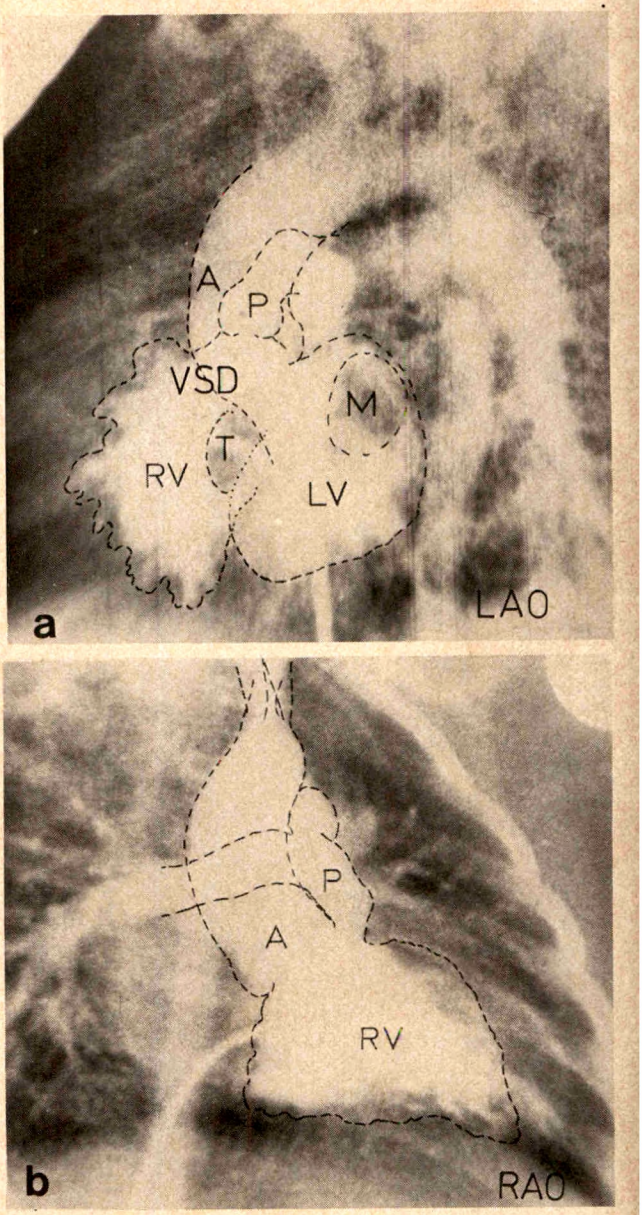


FIGURE 12. Tetralogy variant with absent conal septum. Cine frames after injection in the right ventricle (RV). **a,** diastolic frame in the left anterior oblique (LAO) view; **b,** right anterior oblique (RAO) projection. The aorta (A) and pulmonary artery (P) lie in the normal (aorta rightward and posterior) interrelation. The conal septum is absent; the aortic and pulmonary rings are contiguous and closely related to a high ventricular septal defect (VSD) localized by flow of contrast medium above the tricuspid valve (T) earlier in the study. The basal septum in **a** between the tricuspid and mitral (M) valves is intact and reaches the profiled rightward contour of the aortic valve, indicating its origin from the left ventricle (LV). The pulmonary valve appears to arise from the region of the ventricular septal defect, possibly more from the left ventricle, although the anterior and rightward margin in **a** arises from the right ventricular free wall. At operation, the pulmonary ring was found to arise from the right ventricular side of the ventricular septal defect.

view of double outlet left ventricle because we believe it is difficult to argue effectively in favor of this diagnosis over double outlet right ventricle. We believe that such cases could be categorized as having "ventricular septal defect with overriding of both great arteries" and the classification dilemma expressed in the short term "double outlet both ventricles." These cases have a bilaterally deficient distal conus and absent or deficient conal septum. However, similar conal anatomy may be seen in unequivocal cases of double outlet left ventricle as previously reported[2] and as shown in our Case 2. The rotation and leftward or rightward positioning of the semilunar valves relative to the sinus septum determine their connections, and seem to be influenced by other factors, not merely the type of conus.

The differentiation of patients with double outlet both ventricles from those with "tetralogy" with small or absent crista[17,18] is difficult and sometimes arbitrary, depending on small differences in the relations of the semilunar valve rings to the edges of the ventricular septal defect (Fig. 12). The distinction between this type of tetralogy and double outlet both ventricles is rather academic because the surgical management is similar, and unlike that for true double outlet left ventricle.

Unusual Cardiac Position

Even when the heart lies in an unusual position, as in our Case 3 with visceroatrial situs solitus and dextrocardia, application of the segmental approach with cineangiocardiographic identification of the ventricular morphologic features and the anatomic details and relations discussed in relation to normally positioned ventricles can lead to a confident preoperative diagnosis of double outlet left ventricle (Fig. 4).

Surgical Management

Radiologic assessment of the morphology of the pulmonary stenosis is of value in suggesting the surgical possibilities. The presence of severe pulmonary stenosis at subvalve or valve ring level, or both, combined with a posterior position of the pulmonary ring, makes direct relief of the pulmonary stenosis impossible. Under these circumstances the pulmonary outflow must be closed off and the stenosis bypassed with an external conduit.[19] Fortunately, in most cases the aortic-left ventricular relation is identical to that present in tetralogy of Fallot so that the ventricular septal defect can be closed to establish a normal series circulation and the conduit connects the pulmonary artery to the right ventricle.

When there is no pulmonary stenosis, or when it can be relieved directly, it may be possible to close the ventricular septal defect so that the pulmonary artery is connected to the right ventricle, thus avoiding the need for a conduit pulmonary artery. This was accomplished in the first reported repair[1] but is possible only if the pulmonary artery is suitably related to the ventricular septal defect.

When the ventricular septal defect is subaortic and the pulmonary stenosis can be relieved directly, an external conduit can theoretically be avoided by leaving the pulmonary artery in the left ventricle and closing the ventricular septal defect to connect the aorta to the right ventricle. An atrial baffle repair[20] would then be necessary in addition, in patients with normal atrioventricular connection. Unfortunately, in our experience, this operation is seldom feasible unless the degree of aortic overriding exceeds 50 percent in which instance the patient would be considered to have transposition of the great arteries rather than double outlet left ventricle.

Our Case 5 is of special interest being the first reported case to our knowledge of double outlet left ventricle with visceroatrial situs inversus and a discordant *d*-loop.[21] This case also illustrates the importance of knowing all the connections through the heart before planning surgery. As the pulmonary stenosis could be relieved directly, the repair consisted of a one-step closure of the ventricular septal defect so that the aorta was connected to the right ventricle. Because of the atrioventricular discordance an atrial baffle was not required.

Types of Double Outlet Left Ventricle

Double outlet left ventricle can be classified according to segmental connections, cardiac position, the variety of associated intracardiac features or the great artery interrelationships. Double outlet left ventricle has been reported in situs solitus and, with our Case 5, in situs inversus. Atrioventricular discordance was also present in Case 5, thus making it a rare exception to the well known association of discordant ventricular loop with transposition of the great arteries.[22] All the other known cases of double outlet left ventricle have had atrioventricular concordance. Double outlet left ventricle has not yet been described with a ventricular *l*-loop. One patient, our Case 3, had isolated dextrocardia.

The conal anatomy described in double outlet left ventricle is variable. The most common shows a near normal deficiency of subaortic conal muscle and a short, usually stenotic subpulmonary conus. There was probably a large subpulmonary conus in Case 2 of Pacifico et al.,[4] and their Case 4 may have had a subaortic conus. A short subaortic conus was present in two further cases.[7] Bilateral absence of subaortic and subpulmonary conal muscle has been documented in two cases (Paul et al.[2] and our Case 2).

In all the reported cases but one[2] there was a ventricular septal defect. These have commonly been subaortic in position as in our cases. In one patient[4] there were additional muscular defects, and in another[4] the defect was described as posterior, restrictive and overhung by the tricuspid valve. A subpulmonary defect has been described in one patient.[1]

Pulmonary stenosis, valvular or subvalvular, has been present in most patients. The three cases without pulmonary stenosis were the first two reported[1,2] and Case 3 of Pacifico et al.[4]

Various positions of the great arteries have been found in double outlet left ventricle. In most there was *d*-malposition of the great arteries with the aorta to the right of the pulmonary artery, sometimes side by side, sometimes rightward and anterior or posterior. In our Case 3 and three others[4,7] there was *l*-malposition with the aorta to the left.

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Addendum

Since preparation of this manuscript the authors have become aware of three further publications reporting cases of double outlet left ventricle. [23-25] Case 3 has been reviewed and the patient was catheterized 3 years, 8 months postoperatively. She is progressing well and had at study normal hemodynamics apart from a right ventriclar systolic pressure of 36 to 40 mm Hg and a 16 mm Hg gradient between the right ventricle and pulmonary arteries.

Congenitally Corrected Transposition of the Great Arteries: Morphologic Study of 32 Cases

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The detailed anatomy of the heart is described in 32 autopsy cases of congenitally corrected transposition of the great arteries. This condition is defined as the combination of atrioventricular (A-V) discordance and transposition of the great arteries. Examples of primitive (single) ventricle with "inverted" (that is, left-sided in situs solitus) outlet chamber are excluded. Six hearts with A-V discordance and pulmonary atresia are described in an appendix. In 29 cases of corrected transposition the heart was in situs solitus; in 3 it was in situs inversus totalis. Only 5 of these 32 hearts had no potential for intracardiac shunting. Anomalies of the tricuspid valve (91 percent of cases), ventricular septal defect (78 percent) and pulmonary outflow tract obstruction (44 percent) occurred with sufficient frequency to be considered part of the basic malformation and are described in detail. The precise anatomy and disposition of the A-V valve tension apparatus, the coronary arteries and the conducting tissues are described with special reference to possible surgical approaches for repair of the anomalies. In two hearts with situs solitus the aortic valve was right-sided with respect to the pulmonary valve. This finding is important for both diagnosis and nomenclature.

In previous years surgeons have tended to avoid operative correction of congenitally corrected transposition of the great arteries in view of the known great risk of traumatic heart block.[1–3] However, recent investigators[4–6] have elucidated the unusual disposition of conducting tissues in this anomaly, and subsequent surgeons,[7–9] guided by direct intraoperative identification of the atrioventricular (A-V) bundle, have successfully treated the malformation. Since the "corrected" nature of the circulation in the condition renders its associated anomalies[10] particularly susceptible to surgical repair, it follows that a precise knowledge of the morphologic features of the heart is a desirable prerequisite for successful correction. Surprisingly, few investigators other than Lev and Rowlatt[11] have studied the anatomy in a large series of autopsy specimens. For this reason we describe our finding in 32 autopsy cases of congenitally corrected transposition of the great arteries.

Definitions

In this study we define congenitally corrected transposition as the combination of A-V discordance and transposition of the great arteries. A-V discordance implies that the morphologic right atrium drains into the morphologic left ventricle, and the morphologic left atrium into the morphologic right ventricle, irrespective of the positions of these chambers within the thorax. For the definition of transposition we have followed the precept of Van Praagh et al.[12] and required that both great arteries be placed across the septum, to originate from morphologically inappropriate ventricles, irrespective of their positions relative to each other. We have also followed the suggestion of Ruttenberg[13] that all hearts possess two identifiable ventricular sinuses separated by a discrete interventricular septum. We therefore excluded cases of primitive (single) ventricle with, in solitus hearts, a left-sided outlet chamber. Six hearts with pulmonary atresia are described in the Appendix. Since we cannot verify that the pulmonary

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artery in these hearts would indeed have been placed across the septum, they are excluded from the major group.

From these definitions it follows that the A-V relations in the hearts studied were either solitus (S) atria with L-bulboventricular loop, or situs inversus (I) atria with D-bulboventricular loop (Fig. 1). With an L-loop the aortic valve position could either be left-sided in relation to the pulmonary valve (*l*-transposition) or right-sided (*d*-transposition). Similarly, either *d*-transposition or *l*-transposition could exist in association with a D-loop. It is evident, therefore, that the segmental arrangement of the hearts studied could have been {S,L,L}, {S,L,D}, {I,D,D} or {I,D,L} (see Fig. 6).

In indicating the location of the cardiac chambers we have followed the example of Lev and Rowlatt[11] and described them in terms of their normal morphologic features irrespective of their situation. Because chamber location is frequently not normal, we have also indicated the right-left position of the chambers within the thorax.

Material

Thirty-two hearts satisfied our criteria for inclusion as examples of congenitally corrected transposition of the great arteries (Fig. 1, 2 and 3A). We examined six other hearts (four in situs solitus, two in situs inversus) with A-V discordance, identifiable right and left ventricular sinuses and pulmonary atresia. In each of these the aorta arose from the morphologic right ventricle but, because we were uncertain of the origin of the atretic pulmonary artery, the hearts were not considered to represent congenitally corrected transposition and consequently are included only as an appendix to this series (Appendix, Table I). Of the hearts with true congenitally corrected transposition, 29 (90.6 percent) were in situs solitus and 3 (9.4 percent) in situs inversus. All subjects had a spleen, and visceroatrial situs was obvious in all cases. Because not all subjects were hospital patients, a clinical history was not always available. The hearts were obtained from the collections at Hammersmith Hospital (Royal Postgraduate Medical School), London; Brompton Hospital, London; Birmingham Children's Hospital; Royal Liverpool Children's Hospital; Children's Hospital, Sheffield; Grimsby General Hospital; Wilhelmina Gasthuis and Binnengasthuis, Amsterdam; Gemeente Ziekenhuis, Arnhem; and Sint Antonius Ziekenhuis, Utrecht. One of us (S.P.A.) examined all specimens. The anatomic data of these specimens are given diagrammatically in Figure 2. Certain features of some hearts have been described elsewhere.[5,6,14]

Results

In the typical heart with this malformation, the normal right atrium communicates with a morphologic left ventricle through a mitral valve (Fig. 3B). The transposed pulmonary artery arises from the morphologic left ventricle, and pulmonary-mitral fibrous continuity is present (Fig. 4). The normal left atrium communicates through a tricuspid valve with a morphologic right ventricle, from whose infundibulum the aorta arises (Fig. 5). The arrangement of the cardiac chambers is indicated in Figure 6. In hearts with situs solitus and A-V discordance, the transposed aortic valve was to the left of the pulmonary valve in 27 cases (93.1 percent) and to the right in 2 (6.9 percent). In all hearts with situs inversus, the aortic valve was right-sided.

Detailed anatomy of the morphologic left ventricle: The anatomy of this chamber is not merely that of the normal left ventricle in "mirror-image" position. The pulmonary outflow tract is deeply wedged into the chamber so that the mitral valve extends anteriorly in front of the most anterior point of the pulmonary valve. As a consequence, a characteristic anterior recess of the ventricle is produced (Fig. 7A). The mitral valve is ro-

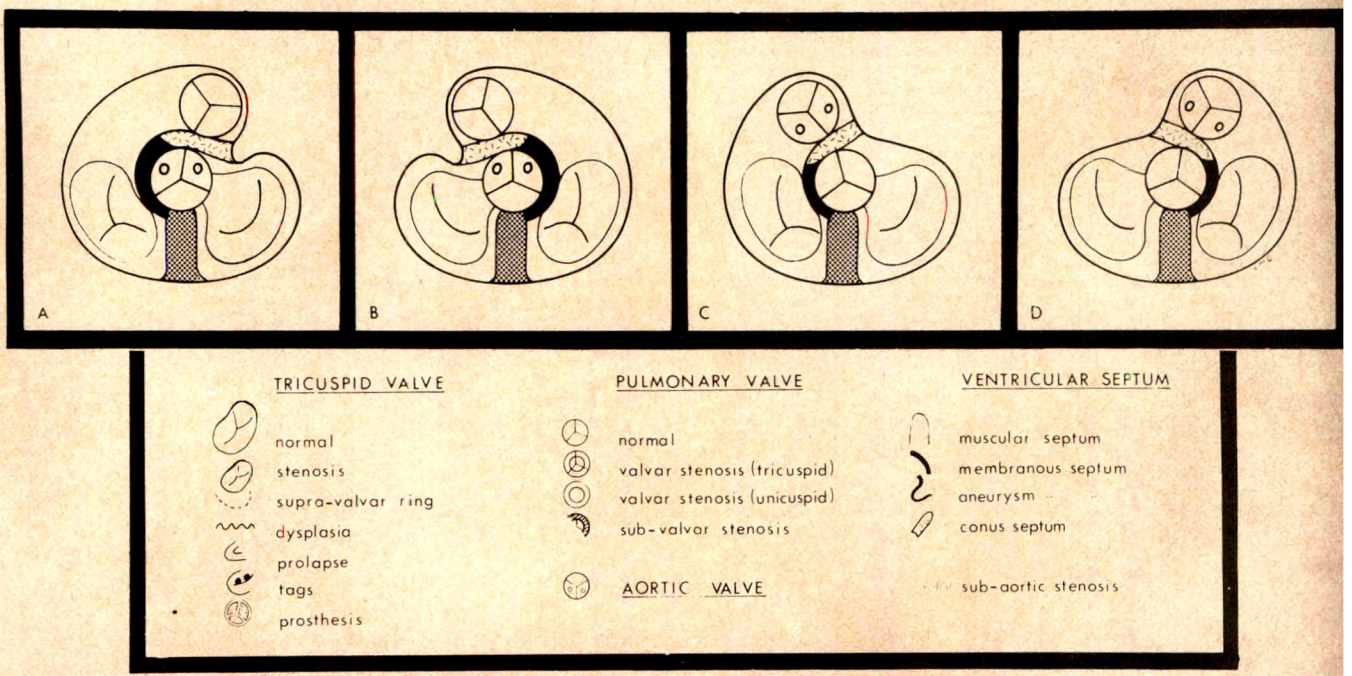


FIGURE 1. Diagrams of the base of the heart, seen from below. **A**, normal heart in situs solitus; **B**, normal heart in situs inversus; **C**, complete transposition in situs solitus; and **D**, congenitally corrected transposition in situs solitus.

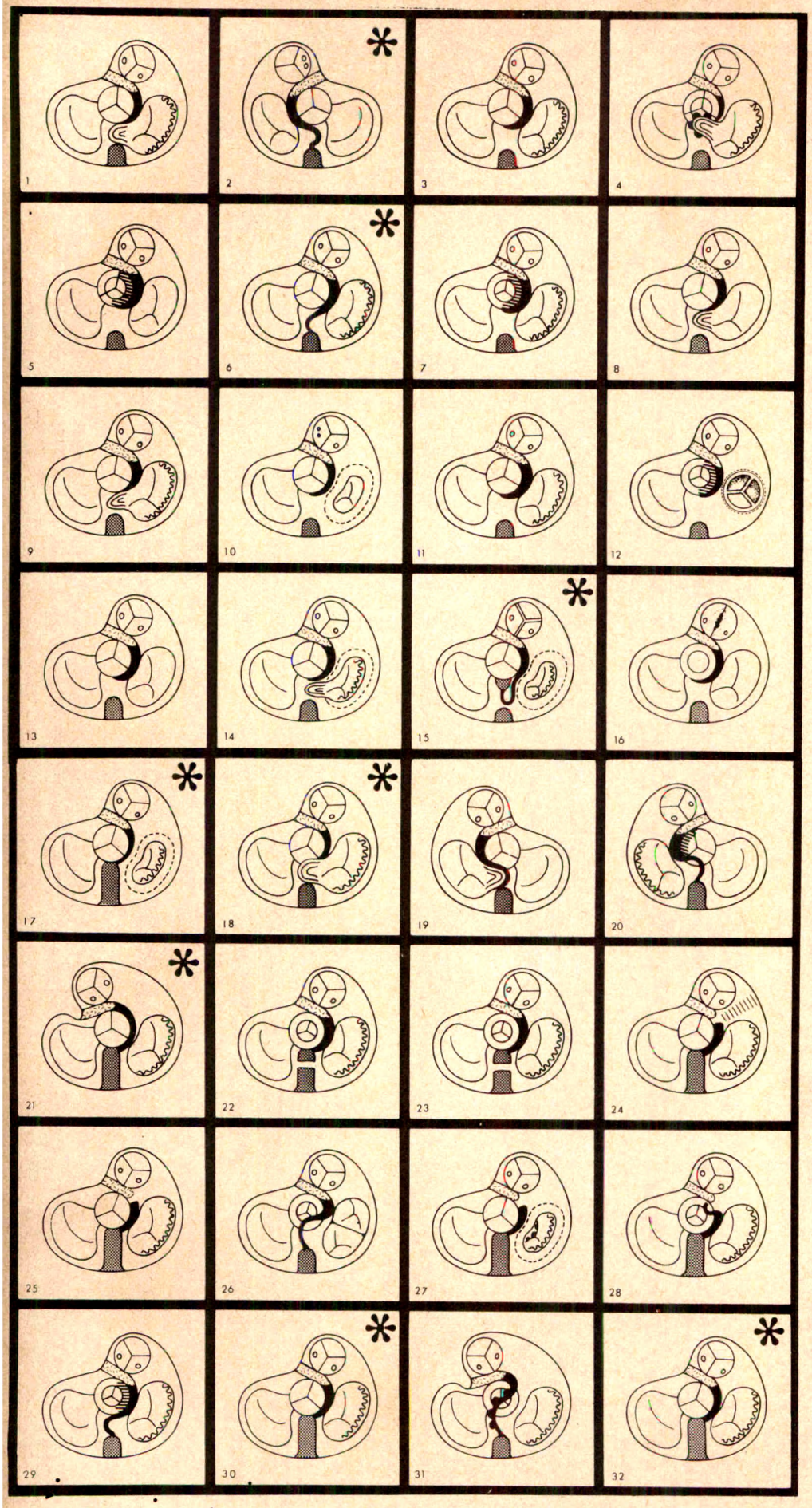


FIGURE 2. Diagram of the base of the heart, seen from below, Cases 1 to 32. Asterisks indicate intact ventricular septum.

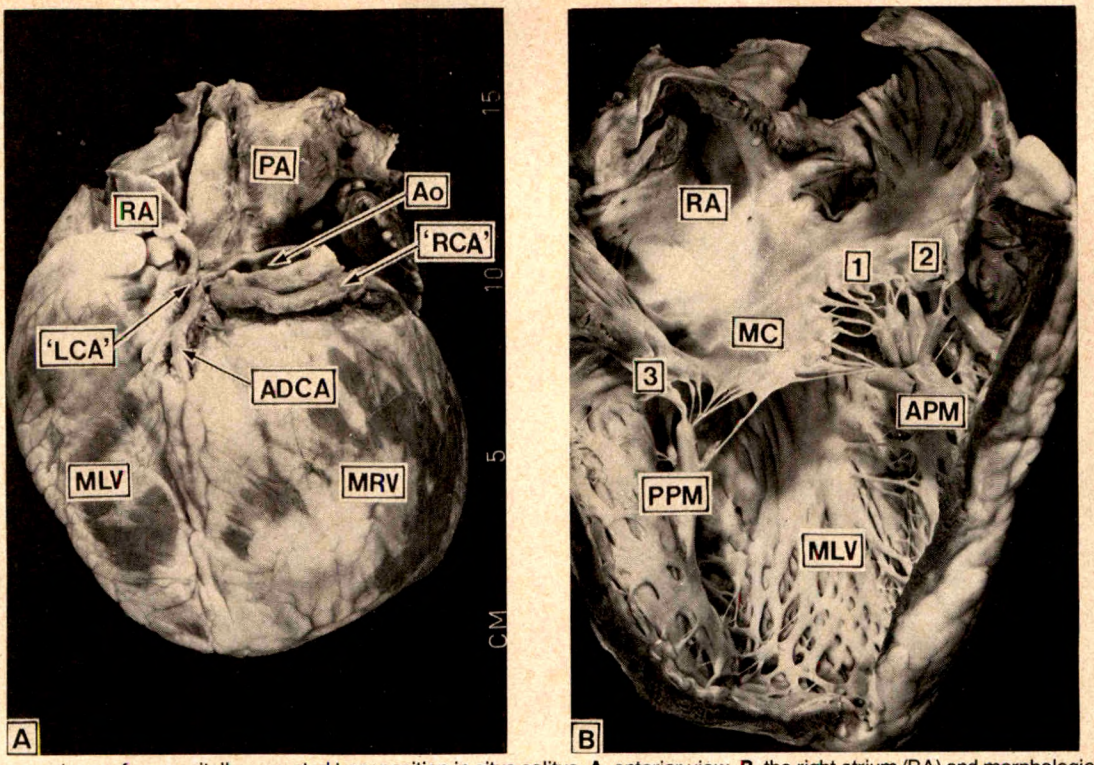


FIGURE 3. Gross anatomy of congenitally corrected transposition in situs solitus. **A**, anterior view. **B**, the right atrium (RA) and morphologic left ventricle (MLV). The scallop appearance of the mitral valve is indicated by the numbers 1, 2 and 3 on the mural leaflet. ADCA = anterior descending coronary artery; Ao = aorta; APM = anterior papillary muscle; 'LCA' = left (circumflex) coronary artery; MC = major cusp of the mitral valve; MRV = morphologic right ventricle; PPM = posterior papillary muscle; 'RCA' = right coronary artery.

tated compared with the normal heart, so that the mural leaflet is anterior and the "aortic" (in these specimens the pulmonary) leaflet is posterior and has fibrous continuity with the pulmonary valve. The anterior leaflet therefore shows the anticipated triple "scallop" appearance (Fig. 3B). The papillary muscle grouping varies correspondingly. The smaller, normally posterior papillary muscles are, in corrected transposition, set in the anteromedial wall of the right-sided left ventricle. Although the muscle group varies in position, measurements in our larger specimens indicated that the muscles were 20 to 50 mm under and anteromedial to the right atrial appendage and 20 to 40 mm to the right of the anterior descending coronary artery (see later). This group of muscles is frequently supplied by large branches of the anterior descending artery. In hearts from children, the muscle group was 10 to 30 mm below the right atrial appendage. The posterior major papillary muscle group was set in a posteroinferior position in the posterolateral wall of the chamber. It was variable in appearance, consisting of a single large muscle in some hearts but of several small muscles in others. The pulmonary outflow tract is obscured by the posterior major cusp of the mitral valve, and retraction of this cusp is necessary to visualize the pulmonary valve and membranous septum (Fig. 7). As in the normally oriented left ventricle, the upper third of the septum is smooth and the apical portion is finely trabeculated, although these trabeculae tend to be coarser than in the normal left ventricle. Unlike the normal left ventricle, in fixed specimens, the A-V bundle and left bundle

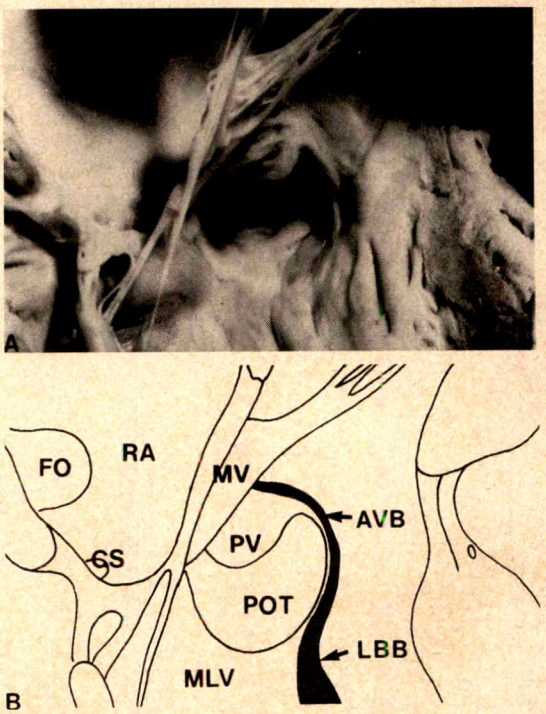


FIGURE 4. The pulmonary outflow tract in congenitally corrected transposition (solitus). **A**, close-up view. **B**, drawing of A. Pulmonary-mitral valve continuity is present. The pulmonary outflow tract (POT) is unobstructed. The atrioventricular bundle (AVB) is seen encircling the pulmonary valve (PV) and extending over the anterior ventricular septum. CS = coronary sinus; FO = foramen ovale; LBB = left bundle branch; MLV = morphologic left ventricle; MV = mitral valve; RA = right atrium.

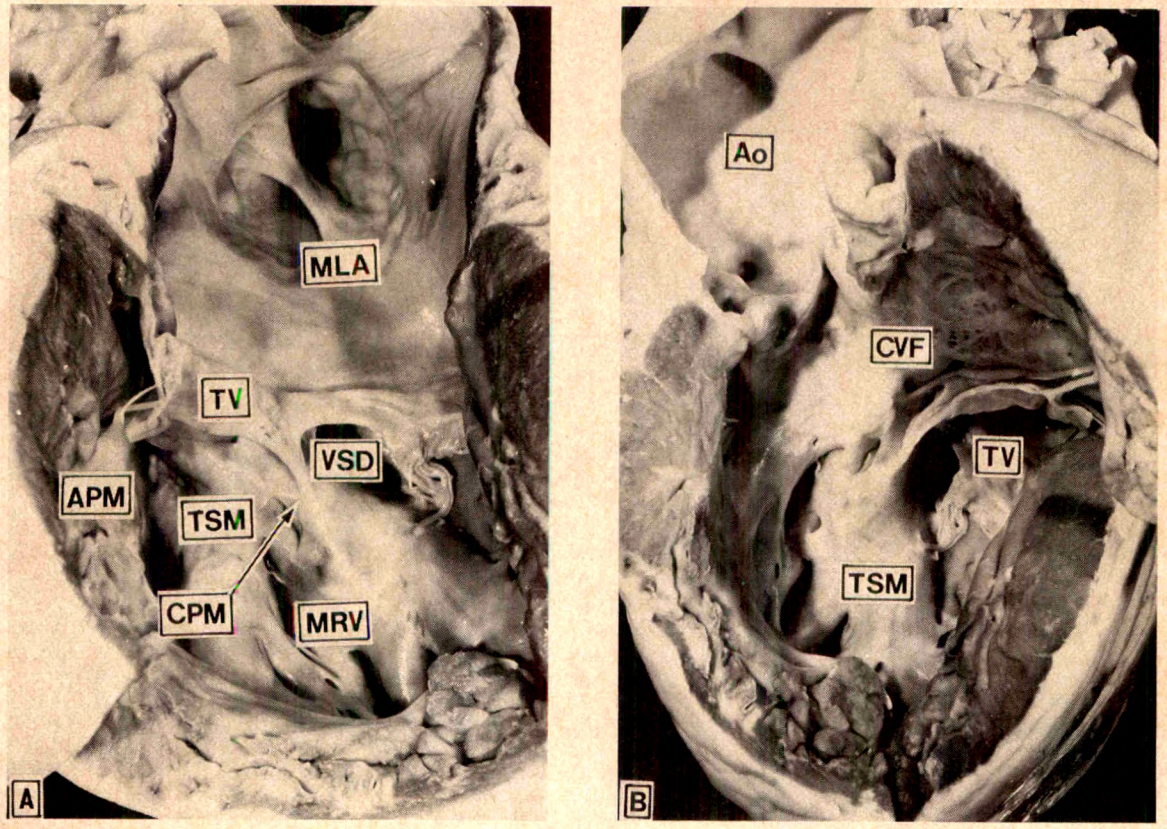


FIGURE 5. Morphologic right ventricle in congenitally corrected transposition. **A**, morphologic (normal) left atrium (MLA) and inflow portion of the morphologic right ventricle (MRV). **B**, outflow portion of morphologic right ventricle. Ao = aorta; APM = anterior papillary muscle; CPM = conal papillary muscle; CVF = conoventricular flange; TSM = trabecula septomarginalis; TV = tricuspid valve; VSD = ventricular septal defect.

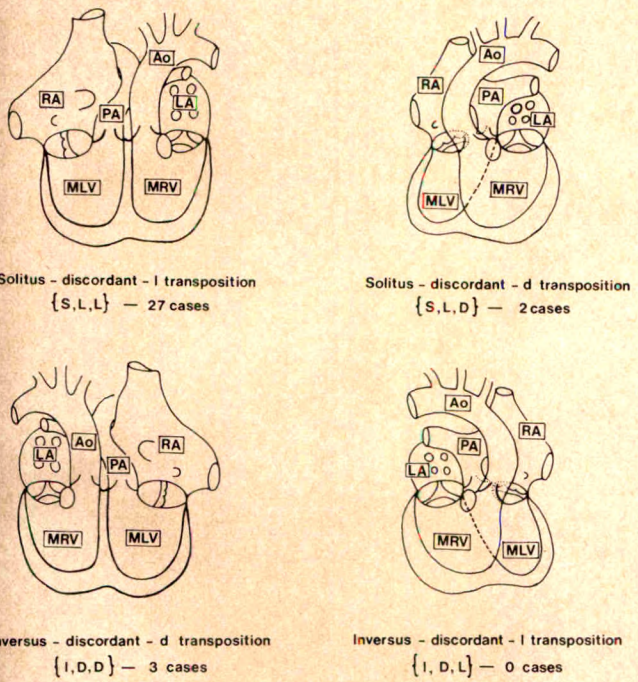


FIGURE 6. Location of the cardiac chambers and the interrelation of the great arteries in 32 cases of congenitally corrected transposition. Abbreviations as in Figures 3 and 5.

branch are frequently visible to the naked eye in an anterior position, encircling the pulmonary outflow tract (Fig. 4 and 7C).

Detailed anatomy of the morphologic right ventricle: As in the normal right ventricle, both inflow and outflow portions are recognized, the two being separated by a crista supraventricularis. The tricuspid valve is not rotated to the same degree as the mitral valve. Posterior, medial (septal) and anterior leaflets are present. The posterior cusp has chordal and, frequently, papillary muscle attachments to the posterior ventricular wall. The septal leaflet is usually related to the papillary muscle of the conus and a large anterior papillary muscle group, arising from the trabecula septomarginalis, tethers both the septal and anterior leaflets. The trabecula septomarginalis forms a prominent septal structure and bifurcates superiorly as in the normal right ventricle; the conal papillary muscle arises from its posterior limb. This muscle is frequently represented by a tendinous cord.

Detailed anatomy of the "membranous septum": Atrioventricular and interventricular portions of this septum are recognized. However, unlike conditions in the normal heart, the A-V portion interposes between the left atrium and the morphologic left ventricle, as illustrated by Walmsley.[15] The interventricular portion

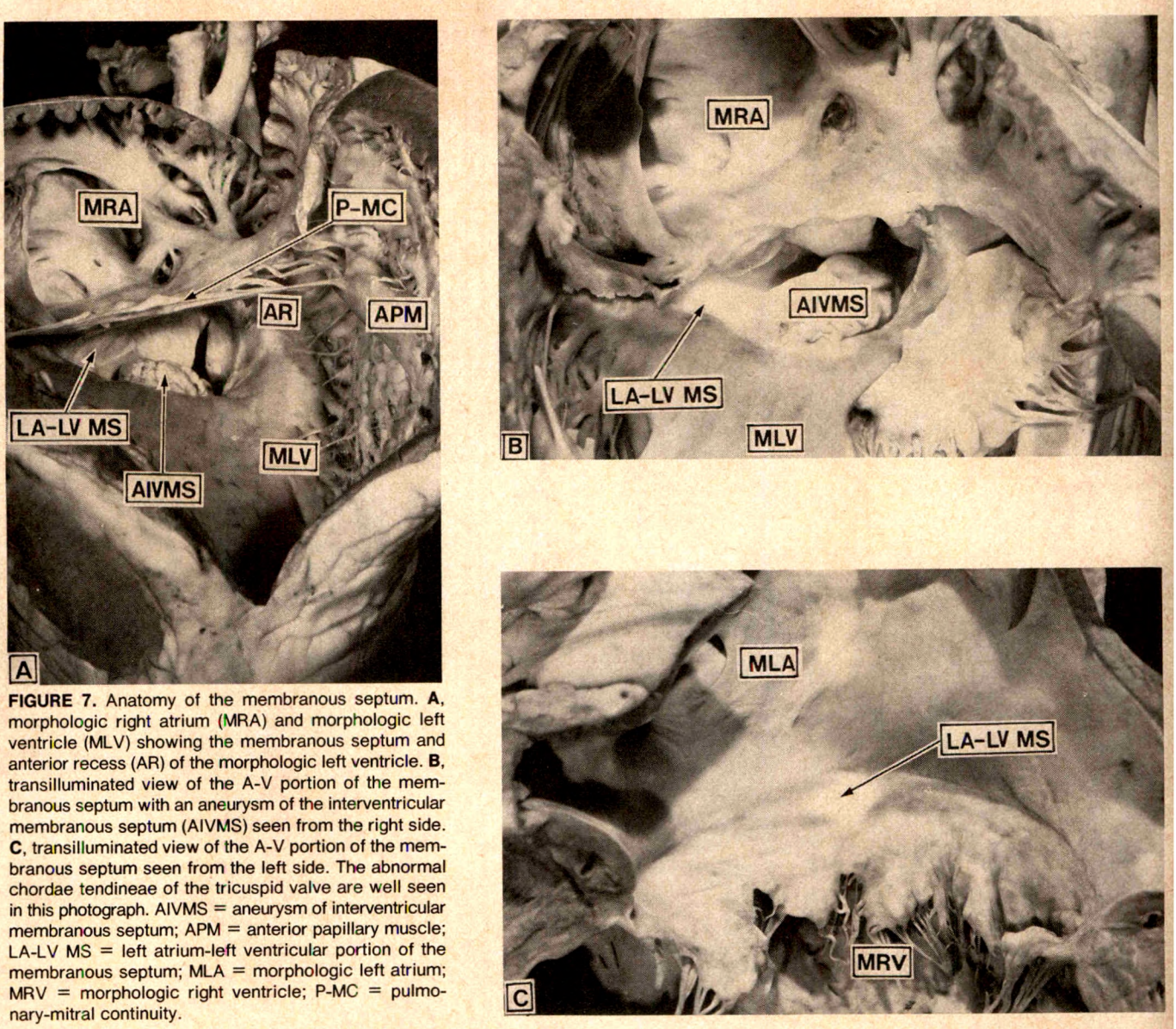


FIGURE 7. Anatomy of the membranous septum. **A**, morphologic right atrium (MRA) and morphologic left ventricle (MLV) showing the membranous septum and anterior recess (AR) of the morphologic left ventricle. **B**, transilluminated view of the A-V portion of the membranous septum with an aneurysm of the interventricular membranous septum (AIVMS) seen from the right side. **C**, transilluminated view of the A-V portion of the membranous septum seen from the left side. The abnormal chordae tendineae of the tricuspid valve are well seen in this photograph. AIVMS = aneurysm of interventricular membranous septum; APM = anterior papillary muscle; LA-LV MS = left atrium-left ventricular portion of the membranous septum; MLA = morphologic left atrium; MRV = morphologic right ventricle; P-MC = pulmonary-mitral continuity.

of the membranous septum is much larger than that in the normal heart owing to the malalignment between the interatrial and interventricular septums in this disorder[5,6] (Fig. 7).

Disposition of the coronary arteries: The coronary arteries in corrected transposition of the great arteries demonstrate the anatomy appropriate to their ventricles; that is, the anterior descending and circumflex arteries supply the anatomically left ventricle, as in the normal heart, and the right coronary artery belongs to the morphologic right ventricle. However, their aortic origins are peculiar to the malformation if one bears in mind that, as in all transpositions, the noncoronary sinus is the anterior sinus of the aortic valve.

In the heart in situs solitus, the anterior descending and circumflex arteries usually arise by a common stem from the right posterior aortic sinus. In one heart in situs solitus (Case 22) the circumflex artery was absent, and in another (Case 10) the anterior descending and circumflex arteries arose from separate ostia in the right posterior sinus. The anterior descending coronary artery emerges from beneath the tip of the right atrial appendage and follows the interventricular sulcus downward and to the right. The circumflex coronary artery arises from the main stem and passes to the right in the right A-V groove. The descending branches arise in the normal manner, but in one heart (Case 17) the circumflex artery gave origin to a particularly large number of muscular branches, quite close together, throughout its course.

The coronary artery supplying the morphologic right ventricle has its ostium in the left posterior aortic sinus, and has the pattern of distribution of a right coronary artery in the normal subject. In one heart (Case 4) a large number of muscular branches were given off along the length of this artery, and in two hearts (Cases 13 and

18) very large conal coronary arteries arose from it. The artery supplying the morphologic right ventricle generally terminated as the posterior descending coronary artery, as in the normal heart.

In the three hearts with situs inversus, the distribution of the coronary arteries appeared at first sight to be identical with that of the normal heart; however, the anterior descending coronary artery, following the interventricular sulcus in the normal manner, arose from the left posterior aortic sinus, not the left anterolateral sinus as in the normal heart in situs inversus. The right coronary artery arose from the right posterior aortic sinus. This pattern was seen in two of the three hearts, but in one (Case 2) the anterior descending and right coronary arteries originated from two ostia in the left posterior aortic sinus and a large conal coronary artery was present.

Disposition of the conducting tissues: A detailed description of the course of the conducting tissues in 11 of the hearts has appeared elsewhere.[6] In the remaining hearts it was frequently possible on gross inspection to confirm the anterior position of the A-V bundle and to observe the relation of the bundle to the anterolateral quadrant of the pulmonary outflow tract (Fig. 4 and 8). The relation of the bundle to septal defects will be described later.

Associated defects: Ventricular septal defects, pulmonary obstruction and tricuspid valve malformations are so frequent in corrected transposition of the great arteries that they may be considered part of the malformation.[10,15] Discussion of these abnormalities will therefore precede discussion of associated anomalies.

Defect of the ventricular septum: Defects were present in 25 of the 32 hearts (78.1 percent). Because of the malalignment usually seen between the interatrial and interventricular septums in congenitally corrected transposition, the majority of these defects were due to incomplete closure of the malalignment gap by the interventricular portion of the membranous septum (Fig. 9).

Malalignment defects were present in 21 hearts (84 percent), and 2 of these (Cases 27 and 28) also demonstrated defects of the conal septum.

Defect of the conal septum occurred in two hearts (Cases 24 and 25) without malalignment defect, and a muscular defect was present in Cases 22 and 23. In Case 15, both malalignment and muscular defects of the ventricular septum were demonstrated angiocardiographically when the patient was 7 years old, but both defects had closed in the intervening 8 years.

Aneurysm of the membranous septum occurred in eight specimens (25 percent) (Fig. 7A). In Cases 15 and 20, the aneurysm occluded the septal defect completely; in Case 2, the ventricular septum was intact and there was an aneurysm of the membranous septum measuring 11 by 8 mm. The ventricular septal defect was wholly or partly occluded by tricuspid valve tissue in 7 of the 25 specimens, and this tissue was seen together with

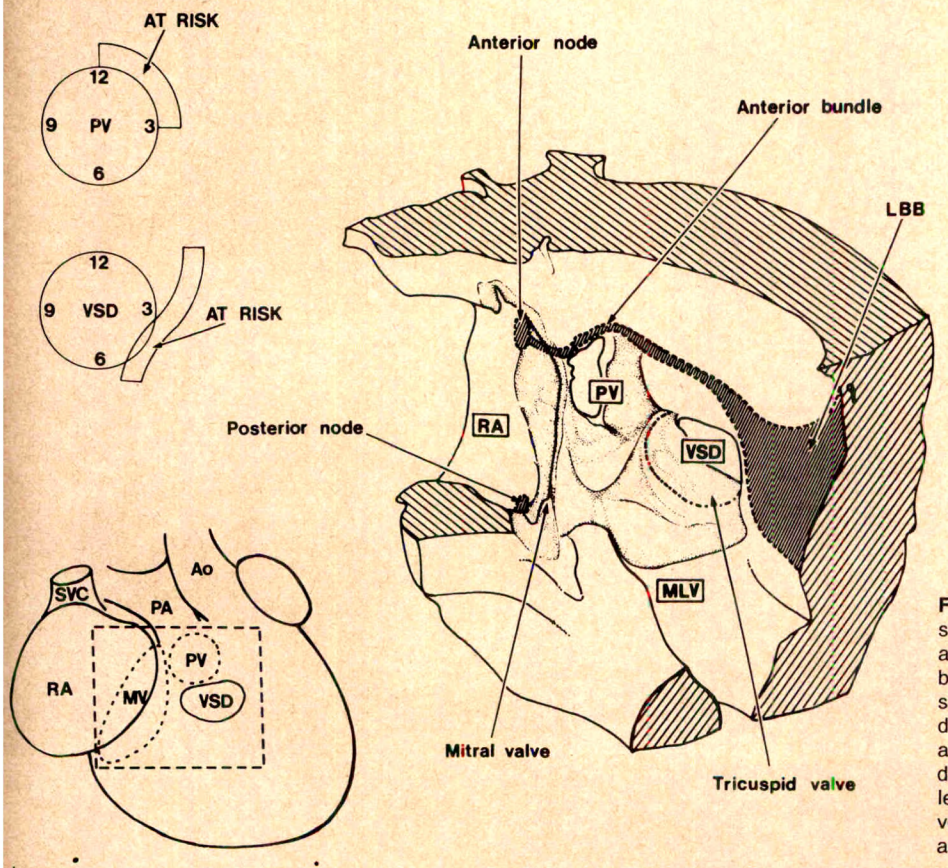


FIGURE 8. The large drawing is a reconstruction by one of us (R.H.A.) of the position and relation of the anterior node and A-V bundle. The extent of the reconstruction is shown at the lower left. The clock figures indicate the areas of the pulmonary outflow tract and ventricular septal defect (VSD) at risk during surgical intervention (see text). LBB = left bundle branch; MLV = morphologic left ventricle; PV = pulmonary valve; RA = right atrium.

aneurysm of the membranous septum in Case 6. Total or partial occlusion of the ventricular defect by fibrous tissue occurred therefore in 9 of the 25 specimens (Fig. 9).

Relation of the conducting system to the defect of the ventricular septum: The penetrating part of the A-V bundle emerges from the anterior node at the lateral border of the area where the pulmonary and mitral valve are in continuity in the morphologic left ventricle. It then passes laterally to the anterior roof of the pulmonary outflow tract, inferior to the ring of the pulmonary valve, which it encircles laterally, descending anteriorly to reach the muscular ventricular septum. Here it descends anteriorly and slightly to the right. If a defect of the ventricular septum is present, the bundle is related to the anterior margin of the defect. In hearts in which the bundle was visible with the naked eye, it was never more than 3 mm from the anterior rim of the defect; this was also true in hearts with an aneurysm of the membranous septum.

When a ventricular septal defect is present, the bundle bifurcates into left and right bundle branches on the anterior aspect of the inferior rim of the defect (Fig. 8). If the ventricular septum is intact, the bundle bifurcates at the anterior summit of the muscular septum. The morphologic left bundle branch passes downward, anterior and to the left, to divide into smaller branches in the middle and lower thirds of the septum. The morphologic right bundle branch, represented by a slender thread or cord-like bundle, passes into the morphologic right ventricle either below or anterior to the papillary muscle of the conus (muscle of Lancisi). The conducting tissue bundle divides and fans out widely over the anterior trabeculae of the morphologic right ventricle.

Abnormalities of the pulmonary outflow tract: The pulmonary outflow tracts of certain of these specimens have been described elsewhere.[14] Obstruction to the pulmonary outflow tract occurred in 14 hearts (43.7 percent). Three had pulmonary valve stenosis only (9.3 percent) ond one of these, Case 16, had a unicuspid pulmonary valve. Nine hearts had both valve and subvalvular obstruction (28 percent) and two (6 percent) had subvalvular obstruction alone. In one of these (Case 18) the pulmonary outflow tract obstruction was due to grossly abnormal calcified tricuspid valve tissue.

Subvalvular pulmonary outflow tract obstruction was due to aneurysm of the membranous septum (five cases), abnormal tricuspid valve tissue (two cases) or tissue from the pulmonary valve itself (one specimen); in the remaining three cases, it was due to muscle bulging into the morphologic left ventricle.

Since the A-V bundle is close to the defect of the ventricular septum, it also has an intimate relation with obstruction to the pulmonary outflow tract if this is also present.

The tricuspid valve: Anatomic malformation of this valve was the most common anomaly associated with corrected transposition of the great arteries. It was noted in 29 hearts (91 percent), 2 of the 3 hearts with situs inversus and 27 of the 29 with situs solitus. The most common malformation resembled Ebstein's anomaly of the tricuspid valve and was present in 22 specimens (76 percent). It was characterized by short, thickened chordae tendineae anchoring the cusps, particularly the posterior cusp, to the ventricle (Fig. 5A). Nodules were commonly found on the free (apposing) edges of the cusps, which gave the valve a warty appearance. The malformation in which a portion of the morphologic right ventricle is "atrialized" did not occur in this series.

Stenosis or hypoplasia of the tricuspid valve was found in five hearts, and in Case 12 the valve had been replaced with the Starr-Edwards prosthesis. In Case 26 the tricuspid valve had a double orifice. A stenosing ring of fibrous tissue was observed on the left atrial (supravalvular) aspect of the tricuspid valve in five hearts (17.2 percent).

Associated anomalies: *Atrial septal defect or patency of the foramen ovale* occurred in 15 hearts (47 percent), all with a ventricular septal defect; 8 of these hearts (25 percent) also had pulmonary outflow tract obstruction. *The ductus arteriosus* was patent in 9 complete hearts (35 percent), but 6 of the 32 hearts (18 percent) were incomplete with respect to the distal aorta, so that the prevalence rate of patent ductus arteriosus may be greater than 35 percent.

Patent ductus arteriosus and atrial septal defect coexisted in six specimens (18.75 percent), all with a

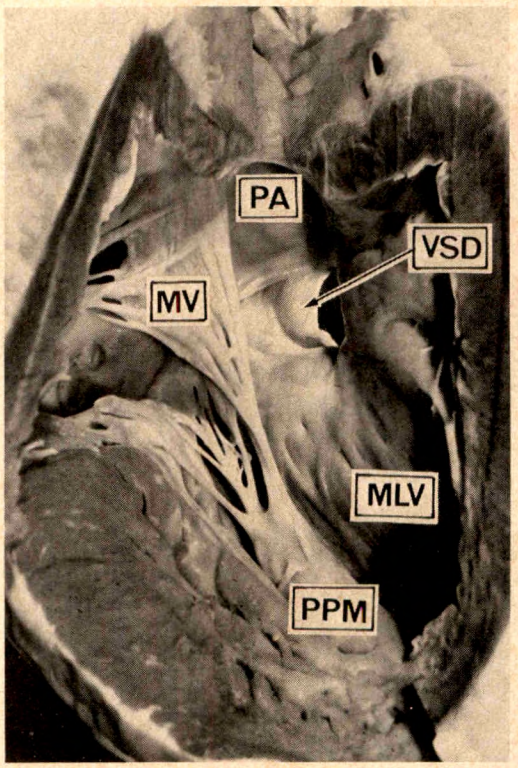


FIGURE 9. Defect of the ventricular septum (VSD) partly occluded by the (incomplete) interventricular membranous septum. The posterior location of the major papillary muscle (PPM) of the mitral valve (MV) is clearly seen. MLV = morphologic left ventricle; PA = pulmonary artery.

ventricular septal defect. Only one of these six hearts (Case 16) had pulmonary outflow tract obstruction, due in this case to a unicuspid pulmonary valve. In Case 27, the ductus arteriosus was patent 2 days before death, but was anatomically closed at necropsy. In Case 25, the ductus arteriosus anastomosed the right subclavian artery with the right pulmonary artery. Hypoplasia of the isthmus was present in four hearts (15 percent of complete specimens); all four had a ventricular septal defect, and three had also an atrial septal defect and two had pulmonary outflow tract obstruction. Anomalies of the aortic valve occurred in three additional cases (9.3 percent), and in two others (Cases 3 and 12) there was a clinical history of aortic regurgitation although the valves were anatomically normal. The heart in Case 16 had severe calcific stenosis of a bicuspid valve; in Case 15 there were thick, but competent cusps and in Case 25 there was infundibular aortic obstruction.

Cases 7, 10, 11 and 13 demonstrated *endocardial fibroelastosis* of the morphologic right ventricle.

Discussion

Classification criteria: Precise definition of "congenitally corrected transposition" has been a contentious topic in recent years. Some consider A-V discordance the hallmark of the anomaly[13] and consider the term congenitally corrected transposition justified only when two ventricular sinuses can be shown to be connected with separate morphologically inappropriate atria. In contrast, other investigators[10,16] give the impression that they consider corrected transposition synonymous with "*l*-transposition" and include examples of primitive (single or common) ventricle with outlet chamber within the category of congenitally corrected transposition. As a result of our study we endorse the first of these concepts as enunciated so clearly by Ruttenberg.[13] We are unable to accept that "*l*-transposition" should be considered an essential part of the anomaly. Our investigation has shown that some hearts with situs solitus and A-V discordance have the transposed aortic valve to the right of the pulmonary valve. Of equal relevance is the demonstration by Carr et al.[17] that the aortic valve is left-sided in approximately 15 percent of hearts with situs solitus, A-V concordance and transposition. We are also unable to define congenitally corrected transposition as "L-loop transposition" since this definition would exclude hearts with transposition associated with situs inversus and A-V discordance. Our study has shown that such hearts are undoubted examples of congenitally corrected transposition. We therefore submit that the only adequate definition of congenitally corrected transposition is the combination of A-V discordance and transposition, the latter defined literally, as suggested by Van Praagh et al.[12]— that is, placement of both great arteries across the septum to arise from morphologically inappropriate ventricles.

It may be argued that such a definition does not exclude hearts with primitive ventricle and left-sided outlet chamber, since they also exhibit A-V discordance. We are unable to accept this contention. In primitive ventricle, both valves drain to a main ventricular chamber whose precise nature is in dispute.[18,19] But whatever its nature, it is clearly improper to use the term concordance or discordance when both atria open to the same chamber irrespective of the position of the outlet chamber. Furthermore, from a surgical standpoint, the absence of a septum in the main ventricular chamber makes primitive ventricle with outlet chamber a considerably more daunting operative prospect than corrected transposition. As Ruttenberg[13] has indicated, primitive ventricle with left-sided outlet chamber is best considered separately from congenitally corrected transposition.

Sex, age and longevity: Following these criteria, we examined 32 hearts with corrected transposition. The patient's sex was known in 24 cases, and males predominated in the ratio of 1.6:1. This finding is in accord with figures previously quoted for both congenitally corrected transposition[16,20–22] and congenitally complete transposition.[23] Our subjects ranged from stillborn to 51 years of age. It has been stated that absence of associated anomalies is essential to longevity,[16,24] and our two oldest subjects had no intracardiac shunt. However, the third oldest, a man of 48 years (Case 16), had ventricular septal defect, pulmonary stenosis, calcific aortic stenosis, atrial septal defect and persistent ductus arteriosus.

Anatomic Considerations

Associated anomalies: Our results strongly support the proposal of Van Praagh[10] that "associated anomalies" should be considered an essential part of congenitally corrected transposition. Only 5 of the 32 hearts did not have the anatomic features necessary for intracardiac shunting, but all 5 had a dysplastic tricuspid valve. Our findings confirmed that the most common associated anomalies were ventricular septal defect, pulmonary stenosis, tricuspid valve anomalies and conduction disturbances. However, the frequency of tricuspid anomalies was greatest (91 percent of cases), followed by ventricular septal defect (78 percent) and pulmonary stenosis (44 percent). A precise figure for conduction disturbances was unavailable owing to the lack of clinical data, but in those whose clinical history was available, the prevalence of dysrhythmias was great.

Tricuspid valve malfunction: Our observed prevalence rate of dysplasia of the morphologic tricuspid valve is considerably higher than that reported in a previous series.[25] The condition of tricuspid valve malformation in corrected transposition was first reported by Edwards,[26] and his description was exemplified by the case of Becu et al.[27] The anomaly is frequently called Ebstein's anomaly,[27] and indeed our observations are in close accord with the original description by Ebstein.[28,29] Thus the dysplastic valve in corrected transposition is characterized by short thickened chordae tendineae that attach the cusps, particularly the posterior cusp, to the ventricular wall. However, the situation in which part of the morphologic right ventricle becomes "atrialized" was not seen in our hearts. Similarly, Becker et al.,[30] observed that the valve

was dysplastic and showed downward displacement of its posterior and septal cusps but found no "atrialization." It may well be that the pathologic dysplasia observed in our study does not necessarily render the valve incompetent. In our patients with clinical data, a history of "mitral" regurgitation was not prominent. This fact could explain the discrepancy between our large prevalence rate of tricuspid dysplasia (91 percent) and the relatively low rate of tricuspid regurgitation (33 percent) reported by clinical investigators.[16,25] It therefore seems reasonable to suggest that the morphologic tricuspid valve in corrected transposition is anatomically abnormal in the majority of cases but is functionally deficient in only about a third. In five of our hearts a supravalvular stenosing ring was present in the morphologic left atrium above the morphologic tricuspid valve. None of the valves in these hearts exhibited parachute deformity. The classic syndrome of supravalvular ring, parachute valve and coarctation usually involves the morphologic mitral valve in normally oriented hearts.[31,32] Although there is no reason to suppose that a similar complex may not occur in corrected transposition, only one of our five hearts with a supravalvular ring had hypoplasia of the isthmus.

Ventricular septal defect: The majority of the ventricular septal defects encountered in our series were of the malalignment variety (84 percent). We encountered conal septal defects in only four hearts (15 percent of hearts with defects) and two of these accompanied malalignment defects. We are aware of only one additional conal defect reported in the Western literature,[33] whereas Okamura and Konno[34] found four conal defects in a series of six Japanese patients. This difference may reflect a racial difference because absence of the conal septum has been reported in a large proportion of Japanese patients with tetralogy of Fallot.[35] Although by virtue of the septal malalignment seen in corrected transposition[6] most of the defects were large, 36 percent were partially or totally occluded by fibrous tissue (Fig. 7). This tissue was derived from the tricuspid valve in the majority of cases, but from the aneurysmal membranous septum in two hearts. Laennec[36] first described aneurysm of the membranous septum in the normally oriented heart and Summerall et al.[37] described it in corrected transposition. There has been discussion of its origin. Some[37–40] have contended that a partially formed membranous septum becomes aneurysmal during spontaneous closure of small "membranous" ventricular septal defects. Others[41,42] consider the aneurysm to be congenital rather than acquired. Misra et al.[43] and Freedom et al.[44] have produced evidence indicating that the condition may be acquired, and most of our observations tend to support this view. However, in the majority of our cases the defects were closed by the abnormal tricuspid valve, which in some instances was additionally aneurysmal.

Pulmonary outflow tract obstruction: Such obstruction, as in congenitally complete transposition,[45] could arise from multiple sources. The nature of obstruction in some of our cases has already been reported.[14] The remaining cases showed similar anomalies. Thus aneurysmal protrusions from fibrous structures surrounding the outflow tract were the most frequent cause of obstruction. Such aneurysms were previously described by Levy et al.[46] as originating from the morphologic mitral valve. None of the aneurysms in our series had this origin; instead they originated from the membranous septum or tricuspid or pulmonary valve.

Additional findings in our study deserve attention. It is important to realize that the aortic valve can be right-sided with respect to the pulmonary valve in corrected transposition in situs solitus. This can be the consequence of rotation at the ventriculo-conal level[47] or at the A-V level.[48,49] It is of paramount importance to recognize this feature, since one of our patients died as a result of the mistaken assumption that *complete* transposition was present. This emphasizes the necessity of establishing connections at both A-V and ventriculo-arterial levels rather than inferring the former from the latter (the "loop" rule). This "rule" has been shown to be an unreliable guide to A-V connections[17,50] (Fig. 6).

Coronary arteries: In all of our specimens these arteries followed a recognizable pattern previously described as a guide to A-V discordance.[11,51] Thus, coronary arteriography or aortic root opacification may be very helpful in making the diagnosis of corrected transposition.[51] It is of further significance that the course of the anterior descending coronary artery delineated the situation of the septum, a feature of considerable surgical importance. Significant anomalies of the coronary arteries were restricted to absence of the circumflex artery in one heart and multiple large conal branches in three hearts. Large conal branches are fairly common in other forms of congenital heart disease.[52–54]

Anomalies of the aorta: These occurred with some frequency in our hearts. Hypoplasia of the isthmus was present in the heart of four subjects who died in infancy. A patent ductus arteriosus was observed in nine hearts; the ductus was unusually long and sometimes tortuous. It has been suggested[25] that atrial septal defect or patent foramen ovale is uncommonly associated with corrected transposition. In our series, 47 percent had evidence of an interatrial communication.

Surgical Considerations

Until very recently, results of surgical repair of corrected transposition have indicated high mortality and morbidity rates.[1–3] This has been due primarily to traumatic production of heart block, and secondly to division of papillary muscles or coronary arteries. From recent studies that have elucidated the disposition of conducting tissues.[5,6] and from our observations, we suggest that these problems can be overcome. It is known that heart block can occur during preoperative manipulation of the heart.[1] This cannot be avoided, but careful placement of caval cannulas may minimize the hazard of early trauma to the A-V bundle. The connecting A-V node in corrected transposition is usually situated anteriorly in the morphologic right atrial orifice

and is therefore in danger if the caval cannulas are introduced through the right atrial appendage. This damage may be avoided if cannulation is performed through a right atriotomy or if the cannulas are inserted directly into the venae cavae at a distance from the heart, similar to the direct venous cannulation for Mustard's operation.[55]

Selection of site of incision for repair and identification of A-V bundle: The potential success of surgery in corrected transposition may be greatly influenced by the choice of approach to the ventricular septal defect or pulmonary outflow tract. Until recently most surgeons incised the morphologic left ventricle, frequently producing the complications referred to earlier.[1–3] Our study has demonstrated that the situation of the anterior septum is indicated by the anterior descending coronary artery. The site of the anterior papillary muscle of the mitral valve is frequently marked by direct branches from the descending artery, but in all hearts studied a safe plane for incision could be determined between the anterior muscle and the septum. The anterior muscle may also readily be palpated through the right atrium. After incising the morphologic left ventricle, it may be necessary to effect considerable retraction on the mitral valve in order to visualize the defect. Viewed from such an incision, the A-V bundle will encircle the pulmonary outflow tract from "12 o'clock to 3 o'clock" and will be directly related to the anterior rim of the defect from "3 o'clock to 6 o'clock" (Fig. 8).[5,6] If this position is confirmed either by gross inspection, or preferably with intraoperative mapping, recent experience has shown that repair can safely be effected.[7–9] Pulmonary obstruction can also be relieved with use of this approach if we bear in mind that relief of anterior muscular obstruction is absolutely contraindicated. It should also be emphasized that recent studies in our laboratories have demonstrated that in corrected transposition with situs inversus, the A-V bundle may be in posterior position, as in a "normal" ventricular septal defect (unpublished observations). We therefore suggest that approach through the morphologic left ventricle is dependent upon availability of apparatus to identify the A-V bundle during operation.

Approach through morphologic right versus left ventricle: Our observations indicate that approach through the morphologic right ventricle has fewer hazards than other approaches. The conducting tissues are less vulnerable from this approach; the papillary muscles of the tricuspid valve are not at risk from infundibular incision; only conal arteries may be at risk, and these are avoidable. This approach provides good access to malalignment, conal septal and muscular defects. The disadvantage of this approach is that the morphologic right ventricle is the systemic ventricle, and indeed Kinsley et al.[47] attributed death in one of their patients to ventricular failure consequent upon ventriculotomy. However, operations through the systemic ventricle in normally oriented hearts are now well established.[56–59] In corrected transposition, it is also possible to incise the infundibulum, which is a relatively noncontractile area. Closure of ventricular defects in complete transposition with Mustard's operation has been successfully accomplished through similar incisions into the systemic ventricle.[60] Approach through the morphologic right ventricle is particularly to be recommended when intraoperative mapping facilities are unavailable or when the apex of the heart is directed to the right in situs solitus. Okamura and Konno[34] recommend this approach for conal defects but questioned its efficacy for malalignment defects. Our observations, obtained in autopsy material only, suggest that the defects are readily accessible through the infundibular incisions. However, they also indicate that relief of pulmonary outflow tract obstruction is generally impracticable with this approach and that the method should be reserved for hearts without such obstruction.

Other surgical approaches: Other approaches have been suggested for repair of the ventricular defect in corrected transposition. A transatrial route has been suggested,[25] and Ruttenberg[22] briefly considered detachment of the mitral valve to gain access to the pulmonary outflow tract. Skow and Mulder[61] utilized this approach in one patient, but produced nonfatal heart block. In view of the relation of the A-V bundle to this structure, this event is hardly surprising. In our opinion such an approach is inadvisable. If the pulmonary valve is stenotic, it can successfully be incised through the pulmonary artery. However, if the pulmonary obstruction is subvalvular, it and any accompanying defect should be first approached through the morphologic left ventricle, utilizing the precautions mentioned. The important point is to delineate precisely the nature of the obstructive lesion, since it may take origin from either the pulmonary or tricuspid valve. Pulmonary obstruction of multiple origin, and without doubt that due to muscular obstruction, may best be treated by placement of a conduit.

Tricuspid valve repair or replacement: Our studies have indicated that the tricuspid valve is abnormal in almost all hearts with corrected transposition. Left A-V valve incompetence may be masked during life by the presence of an interatrial communication but may become important in the postoperative period, being a possible causal factor in pulmonary edema and systemic ventricular failure. Recently, the tricuspid valve has been replaced successfully using a low profile prosthetic valve.[62] The small size of the morphologic right ventricle in many of our hearts certainly commends the use of low profile prostheses. In one of our specimens the right ventricle was completely filled by a regular Starr-Edwards prosthesis; however, the patient died of heart block that followed removal of anterior subpulmonary muscular obstruction. If the integrity of the tricuspid valve becomes prejudiced by relief of pulmonary outflow tract obstruction (for instance, when the valve itself is aneurysmal), then replacement by a low profile prosthesis should be considered.

APPENDIX

Congenitally Corrected Transposition With Pulmonary Atresia

Six hearts with atrioventricular (A-V) discordance and pulmonary atresia were excluded from the description of congenitally corrected transposition as we were unable to speculate on the ventricular origin of the pulmonary valve.

Anatomic Data

The anatomic data of these six hearts are summarized in Table I. The A-V topography was essentially similar to that of congenitally corrected transposition except for one striking difference. The membranous part of the septum was absent from all six specimens. As has been described in congenitally corrected transposition there is considerable malalignment between the atrial and ventricular septums. In contrast, these septums are much better aligned in the hearts with A-V discordance and pulmonary atresia. Thus, in all six specimens there is the potential for communication between the atrial and the posterior ventricular septums.

Ventricular septal defect: This anatomic feature has several important sequelae that differentiate this condition anatomically from congenitally corrected transposition. The most important of these is the nature of the defect of the ventricular septum. Whereas in the hearts with congenitally corrected transposition the defect of the ventricular septum was primarily of the malalignment type, in the five hearts with pulmonary atresia the defect was in the site of the primary interventricular foramen. In our series, 9 of the 25 hearts with ventricular septal defect exhibited a degree of obstruction by fibrous tissue, but in those with pulmonary atresia, obstruction to the defect occurred only once.

In Case 1 the defect was invisible to the naked eye, but was evident on microscopy; in the remaining five cases it was widely patent. In Case 2, a complete endocardial cushion defect was present. In Cases 3 and 4, the defect was at the superior aspect of the trabecula septomarginalis, and its posterior boundary was formed by A-V valve tissue that inserted into the right-sided summit of the muscular septum in the morphologic left ventricle. In Case 5, the morphologic right ventricle was hypoplastic, and the defect was anterior to the trabecula septomarginalis, that is, was subaortic. In Case 6 the defect was again subaortic and anterior to the trabecula septomarginalis.

Disposition of the coronary arteries: As in the 32 hearts with corrected transposition, the coronary arteries demonstrated the anatomy peculiar to the ventricles. In Case 1, both coronary arteries originated from separate ostia in the left posterior aortic sinus; in the remaining five cases, the origin and distribution were as anticipated for A-V discordance.

Disposition of the conducting tissues: A detailed description of the conducting tissue of Case 1 has appeared elsewhere.[14] The distribution is essentially similar to that in congenitally corrected transposition, and the A-V (penetrating) bundle is intimately related to the atretic pulmonary valve ring.

The greater degree of septal alignment in these hearts may permit communication from a posterior node, and gross examination of the heart in Case 6 suggests that this arrangement may be present. To date, only the heart in Case 5 has been examined histologically and, although both anterior and posterior nodes were present, the penetrating bundle originated from the anterior node only.

Atrioventricular valves: Ebstein's anomaly of the tricuspid valve was observed in Case 4, and this valve was dysplastic in Case 5. In Cases 2, 3 and 5, dysplasia was seen in either the tricuspid component of a common A-V valve or the tricuspid valve itself. Case 4 also had a dysplastic mitral valve

TABLE I

Anatomic Data of 6 Autopsy Hearts With Atrioventricular Discordance and Pulmonary Atresia (Variant Cases of Corrected Transposition)

Case no.	Age (days)	Sex	Situs	VSD	VSD "Sealed" by AMS	VSD "Sealed" by TV	Tricuspid Valve	PFO/ASD	PDA	Coronary Arteries	Remarks
1	2	M	I	0	0	0	N	+	+	Both from 2 ostia in left sinus	Microscopic VSD detected on sectioning the heart. Hypoplastic morphologic left ventricle. R. duct. L. ligamentum arteriosum
2	3	M	S	A-V canal	0	0	Dysplasia of tricuspid component of common A-V valve	A-V canal	+	N	Total anomalous pulmonary venous drainage. Hypoplastic morphologic right ventricle
3	6 mo	M	S	+ V-B foramen	0	0	Dysplastic medial cusp passes through VSD	+	+	N	Mitral-tricuspid continuity through VSD. Mild subaortic obstruction due to accessory tricuspid valve tissue
4	13	F	I	+	0	0	Ebstein malformation	+	+	N	Mitral valve regurgitation
5	20	F	S	+	0	0	Dysplasia	+	+	N	Hypoplastic morphologic right ventricle
6	7	F	S	+	0	0	Dysplasia	+	+	N	? Posterior A-V connection suggested by gross examination

AMS = aneurysm of membranous septum; ASD = atrial septal defect; A-V = atrioventricular; duct. = ductus; I = situs inversus; L. = left; M = male; N = normal; PDA = patent ductus arteriosus; PFO = patent foramen ovale; R. = right; S = situs solitus; TV = tricuspid valve; V-B = ventriculobulbar; VSD = ventricular septal defect.
+ = present; 0 = absent.

with short thickened chordae tendineae attached to a large single papillary muscle in the lateral wall of the morphologic left ventricle.

Comment

These six hearts may be considered to represent a variant of congenitally corrected transposition, but because the ventricular origin of only one great artery was identified, we preferred to exclude them from the description of that disorder.

The range of malformations in these six specimens accords with that described in congenitally corrected transposition, with the exception of hypoplasia of the morphologic right ventricle. Our measurements indicate that this chamber may be relatively small in corrected transposition, but hypoplasia did not occur. Although subjects with corrected transposition ranged in age from infancy to 51 years, the oldest of those with pulmonary atresia was 6 months old. Whereas in congenitally corrected transposition the prevalence rate of defects of the ventricular septum was 78 percent, all hearts with pulmonary atresia had a ventricular septal defect, although one was evident only at microscopic examination. Similarly, in corrected transposition, the prevalence rate of defects of the atrial septum and patency of the ductus arteriosus was 47 and 35 percent, respectively; all hearts with pulmonary atresia exhibited both anomalies.

For these reasons, we consider that A-V discordance with pulmonary atresia represents an even greater surgical challenge than congenitally corrected transposition of the great arteries.

Addendum

Since completion of this communication, Mr. W. P. Cleland replaced the morphologic tricuspid valve with a Starr-Edwards mitral prosthesis in a 24 year old woman with corrected transposition. Her only "associated" anomaly was severe regurgitation of the left A-V valve. The operation was performed at Hammersmith Hospital; the patient made an uneventful recovery.

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SPECIAL STUDY

Candida Myocarditis Without Valvulitis

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Thirty-one patients with systemic candidiasis at postmortem examination were found to have Candida involvement of the myocardium without valvulitis. Retrospective examination of their clinical course demonstrated that a new conduction disturbance was seen in 10, supraventricular arrhythmias in 5, QRS changes mimicking myocardial infarction in 3, and pronounced T wave changes in 13. Hypotension or shock was seen in 13 patients and could not be explained by coexistent bacteremia or blood loss in 8. One patient died suddenly. Of 19 patients with systemic candidiasis without myocardial invasion, 4 had minor T wave changes and one had a supraventricular arrhythmia. Candida invasion of the heart significantly complicates the clinical course in systemic candidiasis and should be suspected when a young person without preexistent heart disease has cultures positive for a Candida organism, a significant arrhythmia, conduction disturbance or other dramatic QRS change. The effect of therapy on Candida invasion of the heart is unknown.

Involvement of the heart by Candida organisms is being recognized more often than in the past. Although Candida endocarditis on prosthetic heart valves has received the most attention,[1] direct involvement of the myocardium by Candida organisms without cardiac valve involvement has received little attention. The recognition of complete atrioventricular (A-V) block secondary to an abscess of the interventricular septum caused by Candida albicans reported from this institution[2] prompted an analysis of the problem of Candida myocarditis without valvulitis.

Methods

Autopsy protocols for the years 1959 to 1974 at the University of Michigan Medical Center were examined for evidence of systemic candidiasis. From January 1959 through August 1972 only slide material was available for reexamination. From September 1972 through December 1974, each case of systemic candidiasis was reviewed with particular attention to involvement of the myocardium. All cases were then assigned to either Group I, those with myocardial involvement, or Group II, those without such involvement, as determined microscopically. Cases in which myocardial involvement was coexistent or secondary to involvement of the valves were excluded. In verified cases the clinical course, serial clinical cardiac observations, electrocardiograms, chest roentgenograms and autopsy material were assessed. The pathologic material was reviewed with specific attention to (1) distribution of mycotic lesions in the heart, (2) extent of involvement of other organ systems, and (3) underlying illness.

Results

Group I (Cases With Myocardial Involvement)

Thirty-one patients with Candida involvement of the heart were identified. Twenty cases were noted in the 14 years from 1959 through 1972, and 11 additional cases in the 2 years from 1973 through 1974 (Table I).

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There were 20 male and 11 female subjects. The mean age at death was 35 years.

Associated cardiac disease: Three patients had cardiac disease before the terminal illness. One had hypertensive heart disease with left bundle branch block and an old myocardial infarction at autopsy. A second patient had rheumatic heart disease and had a mitral valve prosthesis 2 weeks before death. At postmortem examination the prosthesis and adjacent myocardium were free of infection but focal myocardial abscesses were noted. Blood cultures were positive for Candida, but the source of the infection was unknown. Neither patient had a new conduction disturbance or arrhythmia during the terminal illness. One other patient had Libman-Sacks involvement of the mitral valve at autopsy. Two patients were receiving digitalis and had mild T wave abnormalities consistent with use of this agent. No electrolyte or acid-base disorders coincided with the appearance of the electrocardiographic abnormalities.

Predisposing illness: Most patients had been chronically ill for several months before the terminal illness. More than half the patients spent part or all of the terminal illness in an acute care facility where continuous monitoring was carried out. Almost all had multiple indwelling intravenous catheters at the time of death. Antibiotic agents were being given to 27 patients and antineoplastic drugs to 9; 16 were receiving corticosteroids; 11 had undergone a major operative procedure within 2 months of death; 6 had had a minor operative procedure (peritoneal dialysis, arterial shunt, skin graft, among others) within 1 month of death. Ten patients had blood dyscrasias such as leukemia or aplastic anemia; two had solid tissue neoplasm and two had body burns. Three infants had neonatal illnesses (enterocolitis, malabsorption syndrome) (Table I).

Severe hypotension or shock complicated the clinical course in 13, but in 5 no bacteremia was present. In six patients with shock, neither bacteremia nor blood loss was present at the time of shock. One patient died suddenly and unexpectedly. Other modes of death included renal and hepatic failure, gastrointestinal hemorrhage and central nervous system lesions.

Electrocardiographic findings: An electrocardiogram was obtained in 22 patients during the terminal illness. That of only one patient, a neonate, was entirely normal. Thirty-nine distinct electrocardiographic abnormalities were seen in the remaining 21 patients (Table II). T wave abnormalities were the most commonly encountered change and were often dramatic, acute in onset and evolutionary. A major new intraventricular or A-V conduction disturbance was seen in 10 patients (excluding the patient with old left bundle branch block), and 5 experienced supraventricular arrhythmias; 3 patients had new QRS changes mimicking myocardial infarction. Despite the dominant left ventricular myocardial involvement with either focal lesions or multiple microabscesses in all patients, only one patient had ventricular premature beats.

Review of chest roentgenograms was not helpful in defining the cardiac problems encountered. Most patients had significant radiographically demonstrable

TABLE I

Age at Death, Underlying Condition and Organism Recovered

	Group I (Myocarditis) (no. = 31)	Group II (Without Myocarditis) (no. = 19)
Age at death (yr)		
<1	4	1
1–21	6	5
22–65	19	13
>65	2	...
Mean	35	39
Underlying condition		
Blood dyscrasias	10	9
Solid tissue neoplasm	2	...
Postabdominal operation	6	1
Postthoracotomy	1	...
Body burn	2	4
Neonatal disease (respiratory distress syndrome, failure to thrive)	2	...
Mediastinitis	...	1
Enterocolitis	1	2
Protein-losing enteropathy	1	...
Disseminated lupus erythematosus	1	1
Hyperalimentation	...	1
Amyloidosis	1	...
Multiple sclerosis	1	...
Cirrhosis	1	...
Hemophilia	1	...
Diabetes mellitus, renal transplantation	1	...
Candida organism cultured (any site)		
Candida albicans	21	15
Candida tropicalis	5	...
Species not specified	5	4

TABLE II

Electrocardiographic Findings*

Electrocardiographic Findings	Group I (Myocarditis) (no. = 31)	Group II (Without Myocarditis) (no. = 19)
1 No electrocardiogram available during acute illness	9	9
2 Normal	1	4
3 T wave abnormalities	13	4
4 Supraventricular arrhythmia	5	1
5 Left bundle branch block	2	—
6 Nonspecific intraventricular conduction delay	2	—
7 QRS changes (without S-T elevation) mimicking anterior myocardial infarction	3	—
8 1° A-V block	2	—
9 Complete A-V block	1	—
10 Left anterior fascicular block	1	—
11 Right bundle branch block with left anterior fascicular block	1	—
12 Premature ventricular contractions	1	—
13 Right bundle branch block	1	—

*Only new electrocardiographic findings are noted. Twenty-two patients in Group I had electrocardiograms during the terminal illness. The abnormalities are not mutually exclusive.

pulmonary disease; however, because portable radiographic equipment was frequently used, estimation of heart size and changes in pulmonary vascularity were difficult to assess.

Group II (Cases Without Myocardial Involvement)

Nineteen patients with systemic candidiasis without myocardial involvement were identified according to the following criteria: positive ante- or post-mortem blood cultures, or microscopic identification of typical organisms located in major organs, excluding the respiratory tract, gastrointestinal tract and urinary bladder. The underlying illness, age of patient at death, and the organism recovered were comparable with findings in Group I (Table I). There were 10 male and 9 female subjects. The mean age at death was 39 years.

Of the available electrocardiograms 40 percent were completely normal, a distinct difference from findings in Group I. Only one major arrhythmia, a transient episode of atrial flutter with variable block, was noted. This occurred 2 weeks before death. No other arrhythmia or major conduction defect occurred in this group. Two of the four patients with minor T wave changes were receiving digitalis; no reason could be found for the minor T wave changes in the other two.

Pathologic Findings

Necropsy demonstrated myocardial abscesses in all 31 cases of Group I. In only seven were gross lesions evident. These consisted of palpable nodules randomly distributed in either ventricle, although most prominent in the left ventricle (Fig. 1). Depending on the age of the lesion, these consisted of 3 to 15 mm white to yellow nodules; in two cases a hyperemic border was evident. A fibrinous pericarditis in various stages of organization was present in 10 cases. In five cases, Candida yeast forms were found.

Histologic examination demonstrated microcolonies of yeast cells forming pseudohyphal extensions in radiating patterns, best identified by silver-methenamine or periodic acid-Schiff reaction (Fig. 2). The extent of the inflammatory reaction varied—from complete absence to well developed acute suppuration—depending upon the patient's underlying disease and immune and cell response capabilities (Fig. 3). The microcolonies infiltrated the endomesial interstitial tissue, spreading

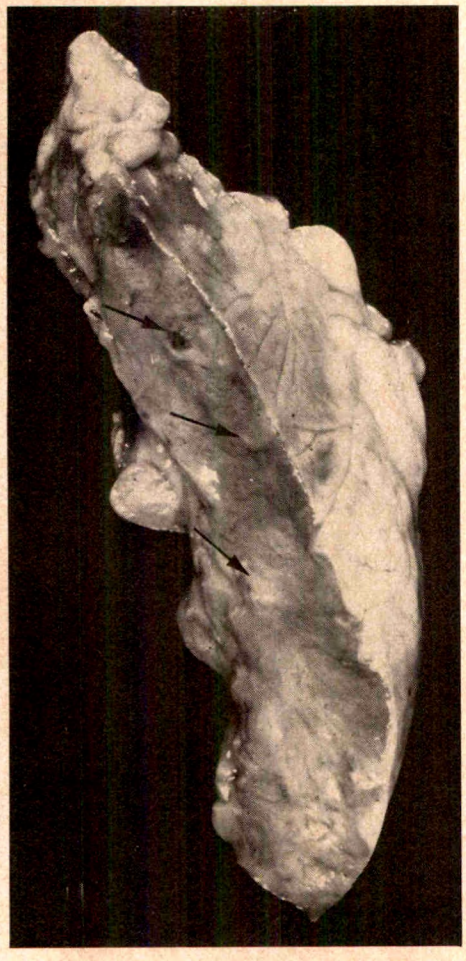


FIGURE 1. Section of left ventricle with multiple gray nodules **(arrows)** representing Candida myocardial abscesses.



FIGURE 2. Left ventricular myocardium containing a microabscess stained with silver-methenamine to demonstrate pseudohyphal extensions of Candida. (Silver methenamine × 285, reduced by 28 percent.)

the myocardial fibers. The intervening myocardial fibers exhibited coagulative necrosis; in some cases, depending upon the inflammatory response, central liquification necrosis formed an abscess. Invasion into blood vessels by pseudohyphae occurred, as is commonly found with aspergillus infections (Fig. 4). This invasion could, in turn, cause local thrombosis within the arteriole itself, or result in progression of the inflammatory process by embolization of the organisms to other areas of the myocardium. Inflammation was restricted to the focal lesion and diffuse myocarditis was not found.

The distribution of lesions to the right or left heart chambers was random, as expected with a septicemic origin, with localizations in mural, epicardial and subendocardial foci. In one case abscesses caused by Candida organisms were found in the conduction system.[2]

In only one case were Candida abscesses restricted to the myocardium and systemic involvement not evident. Focal lesions were present in the kidneys (19 cases), gastrointestinal tract (12 cases), lungs (14 cases), brain (6 cases), liver (6 cases), and thyroid (4 cases). A gastrointestinal lesion was found in 21 of the 31 cases. Candida forms were found as either mycotic plaques or within ulcerative processes.

In 19 of 24 cases with postmortem blood cultures Candida yeast forms were demonstrated.

Discussion

Incidence: Candida involvement of the heart is frequently noted at postmortem examination in patients with systemic candidiasis.[4–9] Of interest is that Candida myocarditis had not been described in the era before the extensive utilization of antibiotic and immunosuppressive agents in clinical practice.[3] There does not appear to be any doubt that the frequency of Candida infections is increasing, particularly in patients with blood dyscrasias.[4,9]

The reported prevalence of cardiac involvement with Candida organisms in patients with systemic candidiasis varies; recent reviews indicate that at least 10 percent[7] and possibly 63 percent of patients[8] have cardiac involvement. Our data are consistent with the higher figure; 31 of 50 patients (62 percent) at our institution with systemic candidiasis had myocardial involvement at postmortem examination. Heretofore, the clinical significance of this involvement was unknown because



FIGURE 3. Myocardium containing a microabscess. A lymphocytic and plasma cell response to proliferating Candida organisms is evident. Coagulative necrosis of myocardial fibers is present at the margins of the abscess. (Hematoxylin-eosin × 120, reduced by 28 percent.)



FIGURE 4. Intramural coronary artery with Candida pseudohyphal ingrowth. No inflammatory reaction is present in this patient with immune-suppression. (Hematoxylin-eosin × 100, reduced by 28 percent.)

there has been no detailed analysis of the clinical course of these patients. Our data indicate that major conduction disturbances and clinically significant arrhythmias result from this involvement.

Cause of hypotension and shock: There are three possible explanations for the hypotension observed in our patients. It may have been due to endotoxic shock from coexistent bacteremia. Septicemia was thought to be present in several patients, but shock often occurred in the absence of gram-negative bacteremia. Although it is possible that hypotension could have resulted from myocardial invasion causing localized or generalized impairment of myocardial contractility, this origin seems unlikely because most patients had small or even only microscopic areas of myocardial involvement. The clinical absence of pulmonary edema also makes this explanation unlikely. It is more likely that hypotension resulted from the release of an endotoxin-like material from the Candida organisms, causing a syndrome pathophysiologically similar to bacteremic endotoxic shock.

Several studies[10–12] have demonstrated that Candida species possess a material similar to bacterial endotoxin capable of producing clinical findings similar to those of bacteremic endotoxic shock. It would appear that substantially greater quantities of the fungal product than the bacterial product are necessary to produce a similar reaction.[12]

Clinical Implications

Our patients differ markedly in all respects from those with Candida endocarditis after intracardiac operative procedures.[1] Only one of our patients had an antecedent cardiac operation. None had new murmurs, gallop sounds, signs of pulmonary edema or embolic phenomena. More than half were immunologically compromised, either by their primary illness or by therapy for it. Nineteen of 31 patients with myocardial involvement were receiving either corticosteroids or antineoplastic agents or both; 27 were receiving one or more antibiotic agents before recovery of the Candida organism.

Although it is not uncommon to recover Candida species from hospitalized patients (0.8 percent of all specimens submitted to one bacteriology laboratory[13]), systemic candidiasis is implicated in very few cases. The death rate in patients with Candida septicemia with systemic candidiasis approaches 100 percent. In our series, as in others, the patients came from many different services of a general hospital; many had indwelling urinary and intravenous catheters and many had received blood transfusions and had minor or major operative procedures.

The electrocardiographic changes described are in no way specific for Candida myocarditis and are similar to those described by Fine et al.[13] in a review of electrocardiographic changes in myocarditis of any origin. Their study also demonstrated that fever as such rarely caused even subtle electrocardiographic changes.

Treatment and diagnosis: Only two patients in this series were treated for systemic candidiasis, and one received only 6 mg of Amphotericin B before death. In a third patient the decision to institute therapy was made just before death. The rarity of premortem diagnosis and timely treatment is surprising because 22 patients had positive sputum, blood or wound cultures during their hospital course. The difficulties of selecting treatment for patients with positive cultures for Candida species have been outlined by several authors.[1,14,15]

Myocardial involvement with the Candida organism should be strongly considered when a patient with positive blood, urine or sputum culture for Candida has a major intraventricular or A-V conduction defect, new QRS changes or an arrhythmia. In fact, with only one exception these new electrocardiographic changes were found to be specific for this. New T wave changes in the absence of digitalis appear to be a sensitive but less specific indicator of myocardial Candida involvement. Inasmuch as ischemic heart disease, electrolyte disturbances, acid-base disorders and some drugs may produce some of the electrocardiographic changes seen here, the degree of suspicion for Candida myocarditis in the patient with systemic candidiasis should be greatest when electrocardiographic changes are seen in the younger patient without preexistent heart disease or other known causes of the electrocardiographic abnormalities.

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Intramuscular Clindamycin for Therapy of Infective Endocarditis

Report of 23 Cases and Review of the Literature

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Twenty-three patients with infective endocarditis received intramuscular clindamycin (Cleocin) for treatment. Thirteen had acute Staphylococcus (S.) aureus endocarditis but none had involvement of the aortic valve. Eleven of these 13 infections were heroin-related and involved the tricuspid valve. Twenty-one patients were successfully treated. Two patients with heroin-related S. aureus infection failed to respond to intramuscularly administered clindamycin, but responded to retreatment with methicillin. There have been 34 additional reported cases of endocarditis treated with clindamycin. Although 80 percent of all cases due to staphylococci responded favorably, almost all were heroin-related tricuspid valve infections. In addition 91 percent of cases due to aerobic streptococci responded but, surprisingly, treatment failed in three of four cases of anaerobic endocarditis. Although clindamycin can be useful in streptococcal endocarditis and in some cases of heroin-related S. aureus tricuspid endocarditis, caution should be exercised in its use. It is "less" bactericidal than the penicillins or cephalosporins, and organisms have become resistant during treatment. Furthermore, patients with anaerobic endocarditis have not responded well, and data are not available to recommend administration of clindamycin for acute S. aureus infections engrafted on the aortic or mitral valve.

In recent years, alternate antibiotic agents were shown to be effective for the treatment of infective endocarditis in patients who could not be given penicillin. Clindamycin (Cleocin®), a bactericidal antibiotic that is not cross-reactive with the penicillins or cephalosporins, is a derivative of lincomycin produced by the chemical replacement of a 7-chloro group for the 7(R) hydroxyl group of lincomycin.[1] In vitro studies showed this agent was four to eight times more active than lincomycin against staphylococci and streptococci (excluding enterococci) and also demonstrated that it was more active against penicillin-resistant staphylococci than the penicillinase-resistant penicillins.[2,3] Recent reports of drug-related pseudomembranous colitis have limited use of clindamycin to treatment of severe anaerobic infections outside the central nervous system caused by Bacteroides (B.) fragilis and some staphylococcal infections in the patient allergic to penicillin.[4]

A preliminary report by our group[5] suggested that clindamycin might be an effective alternate to penicillin for treatment of endocarditis, and Bente and Jackson[6] confirmed its potential value. Subsequently, cases were reported[7–10] in which clindamycin was effectively utilized in the therapy of infective endocarditis, but other reports[11–14] indicated that it was not uniformly successful.

This paper reports the results of intramuscular clindamycin therapy in 23 patients with infective endocarditis treated since 1969 and reviews 34 other reported cases.

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Materials and Methods

Patients: Twenty-three patients with a diagnosis of infective endocarditis were treated with intramuscularly administered clindamycin. Of these, four were allergic to penicillin, five had veins inadequate for prolonged intravenous therapy and four were responding poorly to conventional therapy. In some patients treatment with other antibiotic agents was begun and later discontinued in favor of clindamycin therapy when results of cultures and in vitro studies became available.

Nineteen of the patients were male and four female; the mean age was 38 years (range 4 to 71 years). Twelve of the 23 patients had preexisting valve disease; in these 12 the usual clinical criteria for endocarditis plus the presence of two or more positive blood cultures were required for inclusion in the study. Seven of the 12 had rheumatic heart disease, all with mitral valve involvement alone; 2 had congenital heart disease (1 patent ductus arteriosus and 1 tetralogy of Fallot); the remaining 3 had mitral valve disease as a result, respectively, of prior acute pseudomonas endocarditis, Barlow's syndrome and arteriosclerotic heart disease. Causative organisms in this group of 12 patients included Streptococcus viridans (6 cases), Staphylococcus (S.) epidermidus (1 case), S. aureus (2 cases), nonhemolytic streptococcus (1 case), beta streptococcus (1 case) and B. fragilis (1 case). The latter patient had an associated liver abscess.

Eleven patients, all heroin addicts, had acute S. aureus endocarditis engrafted upon a previously normal tricuspid valve. Diagnosis was made using criteria similar to those defined by Menda and Gorbach.[7] These included (1) persistent bacteremia, (2) cardiac murmur present on admission or developing during treatment, (3) temperature higher than 38.3°C on admission, and (4) evidence of embolization to lungs, kidneys, digits or conjunctiva. Five had radiographic evidence of coexistent septic pulmonary emboli. One had septic arthritis of the knee and sternoclavicular joints; another had involvement of the sternoclavicular joint alone.

Treatment regimens: Clindamycin was given intramuscularly in doses of 450 to 600 mg every 6 to 8 hours for 4 to 8 weeks with five exceptions. One, a 4 year old child, received only 100 mg every 8 hours for 3 weeks after an allergic reaction to cephalothin. Another, a heroin addict, had been treated for only 3 weeks when she left the hospital against medical advice. The third received a second course of clindamycin for 6 weeks after a relapse that occurred after an earlier course of 32 days of treatment. In the remaining two therapy was discontinued at 2 weeks, in one because failure of clindamycin was suspected and in the other because of an allergic reaction attributed to clindamycin.

Each patient was examined and questioned daily for adverse effects such as skin rash, diarrhea and painful injection sites. Serial liver function tests, renal function tests and hematologic profiles were obtained.

Antimicrobial susceptibility tests and bactericidal serum titers: The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of clindamycin for each causative endocarditis organism was determined by the two-fold dilution technique. One cc of 10^{-3} dilution of an 18 hour culture in trypticase soy broth was used as the inoculum. The MIC was defined as the lowest concentration of clindamycin that inhibited visible growth of bacteria after 18 hours of incubation at 37° C. The MBC was defined as the highest dilution from which no more than 50 colonies grew after 0.01 ml was subcultured onto 10 percent sheep's blood agar and incubated overnight.

Bactericidal titers of serum were determined from each patient during treatment using a method similar to that described earlier. Trypticase soy broth was used as the diluent with an inoculum of approximately 10^5 organism of an 18 hour culture.

Results

Of the 23 patients, 21 were cured; the other 2, both heroin addicts with S. aureus, had a recurrence of the infection. One was given another course of clindamycin for 6 weeks and again had a recurrence. Both patients were subsequently cured with intravenous treatment with methicillin, 12 g/day for 6 weeks. After the recurrence, both organisms were still susceptible to clindamycin.

TABLE I

Summary of Reported Cases of Bacterial Endocarditis Treated With Clindamycin

Authors	Organism	no. of Cases	Outcome	Comments
Tuazon and Sheagren[12]	S. aureus	1	Failure	Penicillin allergy; failure with cephalothin; cure with nafcillin after desensitization
Elmore et al.[9]	S. aureus	1	Cured	Penicillin allergy; failure with cephalothin; hepatotoxicity due to clindamycin
Garriques and Duma[11]	S. viridans	1	Failure	Penicillin allergy; cure with penicillin G after desensitization
Menda and Gorbach[7]	S. aureus	14	Failure (3); cured (10); allergic reaction (1)	Cephalothin produced cure in one patient, failed in two others who later had cure with clindamycin (one patient after two 6 week courses)
	S. viridans	1	Cured	
Keane and Rose[10]	S. pneumoniae	1	Cured	Penicillin allergy; required elective prosthetic valve replacement
Hinthorn et al.[13]	S. aureus	1	Cured	
	S. viridans	1	Cured	
	S. epidermidus	1	Cured	Hepatotoxicity due to clindamycin
	Microaerophilec streptococci	2	Failure	
	Peptostreptococcus	1	Failure	Tenfold increase in MIC after relapse
Bente and Jackson[6]	S. aureus	8	Failure (1); cured (7)	
Watanakunakorn[14]	S. aureus	1	Failure	Organism resistant after relapse

MIC = minimal inhibitory concentration.

In four cases, response was inadequate to conventional antibiotic therapy and treatment with clindamycin was begun. All four patients were cured. One patient with S. aureus engrafted on the mitral valve failed to respond after 7 days of administration of cefazolin. Within 72 hours after clindamycin was initiated, the patient was afebrile. Another, a heroin addict with a methicillin-sensitive S. aureus tricuspid endocarditis, had a poor clinical response as well as positive blood cultures after 9 days of intravenous methicillin therapy given in a dose of 12 g/day. He promptly responded clinically and bacteriologically to clindamycin therapy. As we reported elsewhere,[15] a patient with penicillin-resistant (MIC 0.8 μg/ml) Streptococcus viridans endocarditis responded to clindamycin after failure of therapy with intravenously administered ampicillin in a dose of 12 g/day given together with intramuscularly administered streptomycin, 1 to 2 g/day for 6 weeks. The organism was susceptible to clindamycin (MIC 0.024 μg/ml). The fourth patient, with B. fragilis endocarditis, was responding poorly to chloramphenical when treatment with clindamycin was initiated, resulting in prompt resolution of fever and negative blood cultures. Surgical drainage of a solitary liver abscess on the 9th day of therapy may account in part for the success of clindamycin in this patient.

Clindamycin therapy discontinued in favor of other antibiotic agents: Discontinuation of clindamycin therapy was required in two patients. In one, a pericardial effusion developed on the 20th day of clindamycin therapy. Although blood cultures were negative at the time, clindamycin was stopped and therapy was completed with penicillin G for 16 days. Later studies demonstrated that the effusion was due to M. tuberculosis rather than to clindamycin failure.[16]

The other patient with an atopic history manifested skin rash and eosinophilia believed to be secondary to clindamycin. Because of this, the planned 30 day course of therapy was completed using cephaloridine and gentamycin for the final 16 days. The patient was afebrile and blood cultures were negative when clindamycin was discontinued.

Side effects: In two instances, the intramuscular mode of administration was changed to the intravenous route for completion of therapy because the patients complained of painful injections. On examination of injection sites, there was minimal erythema and induration. In all other cases, the intramuscular route was well tolerated. No hematologic or hepatic dysfunction was encountered. Since no patient complained of diarrhea, proctoscopy was not performed to assess the presence of pseudomembranes.

A summary of other reported cases of endocarditis treated with clindamycin is contained in Table I. Table II lists the cumulative percent of our cases plus those previously reported to be cured with clindamycin.

Antimicrobial activity and bactericidal activity in serum: All causative organisms isolated had minimal inhibitory and minimal bactericidal concentrations for clindamycin of 0.8 μg/ml or less. The minimal inhibitory concentration of clindamycin for all streptococci and staphylococci was 0.1 μg/ml or less; for one anaerobe, B. fragilis, it was 0.156 μg/ml.

TABLE II

Cumulative Percent of Cases of Bacterial Endocarditis Cured With Clindamycin

Organism	Total	Cures	%
Staphylococci	40	32	80
Streptococci (aerobic)	12	11	91
Anaerobes			
Penicillin-sensitive	3	0	25
Penicillin-resistant	1	1	...

Using the regimens of clindamycin as described, peak serum bactericidal titers 8 to 1,024 times the minimal inhibitory concentration for each causative organism were obtained in all cases. In two cases failing to respond to clindamycin administration, peak bactericidal titers 64 to 512 and trough titers 16 to 32 times the minimal inhibitory concentration for the infecting organism were achieved.

Discussion

Although penicillin G or a semisynthetic penicillin is the antibiotic of choice for infective endocarditis when the organism is susceptible, antiobiotic therapy for patients allergic to penicillin presents a difficult therapeutic problem. In addition, severely scarred veins of heroin addicts may require intramuscular administration of an antibiotic agent. In recent years, both clindamycin (Cleocin®) and cefazolin have been utilized with some success in these situations.

Clindamycin versus other antibiotics: Generally a bactericidal antibiotic drug is deemed necessary for treatment of infective endocarditis and clindamycin is "less" bactericidal than penicillin G, the semisynthetic penicillins and the cephalosporins but more bactericidal than its parent compound lincomycin.[17] In this study, the minimal inhibitory and minimal bactericidal concentrations of clindamycin for each causative organism plus serum inhibitory and bactericidal titers were similar. Others have noted differences in inhibitory and bactericidal measurements with clindamycin, which has slow bactericidal action.[11,14] Our bactericidal end point of less than 50 persistors differs from that of others,[14] who regard less than 5 persistors as the end point. This difference may account for the failure of two patients in our series with S. aureus endocarditis to respond to clindamycin despite adequate serum bactericidal titers.

Using an animal model of endocarditis in rabbits,[18] Sande and Johnson[19] demonstrated that clindamycin could not sterilize aortic vegetations infected with penicillin-sensitive S. aureus and noted that cefazolin was more effective than penicillin G. Such experimental animal results are difficult to relate to our data. Many cases of S. aureus endocarditis are due to penicillin-resistant organisms and involve only the tricuspid valve in heroin addicts. Such cases are associated with a better prognosis than those not related to heroin abuse, which

usually engraft on the aortic valve.[20] For example, of our 13 cases, 11 were heroin-related and all involved only the tricuspid valve. Two patients with underlying heart disease had S. aureus endocarditis and neither had an infected aortic valve. One had a patent ductus arteriosus with pulmonary stenosis and the other mitral insufficiency. Furthermore, failure of cefazolin has been reported in patients with heroin-related S. aureus tricuspid endocarditis.[21,22] Some strains of staphylococci can degrade cefazolin by production of a beta lactamase.[21] These strains can be identified in vitro by using a high level of innoculum of organisms, that is, (10^7) rather than (10^5).[21] We previously reported cefazolin failure in one patient with endocarditis caused by such an organism,[21] and a similar "inoculum effect" was present in one patient in this series responding poorly to cefazolin. He subsequently was treated successfully with clindamycin.

Potential problems and adverse effects: A potential clinical problem with clindamycin is development of resistance, which can occur after rapid passage of staphylococci in cultures containing the antibiotic.[23] We did not encounter this problem, but Watanakunakorn[14] recently described a patient with S. aureus endocarditis who failed to respond with clindamycin. The organism was clindamycin-resistant at relapse. Also some anaerobic organisms, usually sensitive to clindamycin, have become resistant. Salaki et al.[24] described two patients with bacteremia due to clindamycin-resistant B. fragilis, and Hinthorn et al.[13] reported clindamycin failure in endocarditis due to a penicillin-sensitive peptostreptococcus that became resistant during therapy.

Adverse reactions reported with clindamycin such as colitis and hepatotoxicity were not encountered in our cases. Many factors including the young age of our patients, absence of underlying disease and the intramuscular route of administration may have been important. Colitis is more common in older debilitated patients[25] and occurs more frequently with oral rather than parenteral administration.[26] Further studies are necessary to determine if the intramuscular route of administration may be less toxic than the intravenous.

Review of previously reported cases: There have been reported 34 additional cases of infective endocarditis treated with clindamycin. Although data were not always available to evaluate completely the involved valve or route of administration, 25 cases were due to S. aureus. Of these, the majority were heroin-related and involved only the tricuspid valve. Combining these reports with our cases, 80 percent of cases due to staphylococci and 91 percent of those secondary to aerobic streptococci were cured. Surprisingly only one of four due to anaerobes was cured. Even though overall cure rates for staphylococcal and aerobic streptococcal endocarditis with clindamycin are similar to those reported for the cephalosporins,[27] clindamycin should be used cautiously.

Our data suggest that clindamycin has a limited but valuable use in selected cases of infective endocarditis, particularly as an alternate in penicillin-allergic patients with S. aureus tricuspid endocarditis when intramuscular administration is necessary. Caution is required in its use for mitral or aortic valve endocarditis.

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Clinical Efficacy of Amiodarone as an Antiarrhythmic Agent

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Amiodarone, administered orally in doses of 200 to 600 mg/day, was remarkably effective in the treatment and prevention of a wide variety of atrial and ventricular arrhythmias. Total suppression and control was provided in 98 (92.4 percent) of 106 patients with supraventricular arrhythmias and in 119 (82 percent) of 145 patients with ventricular arrhythmias. The rates of total control of the arrhythmia were: 96.6 percent in 30 patients with recurrent atrial flutter or fibrillation, 96.6 percent in 59 patients with repetitive supraventricular tachycardia, 100 percent in 27 patients with Wolff-Parkinson-White syndrome and 77.2 percent in 44 patients with recurrent ventricular tachycardia unsuccessfully treated with other drugs. Excellent results were obtained in 6 of 8 patients with repetitive ventricular tachycardia and ventricular fibrillation related to postinfarction ventricular aneurysm and in 12 of 14 patients with ventricular extrasystoles and ventricular tachycardia related to Chagasic myocarditis. Amiodarone proved safe in patients with severe congestive heart failure and severe myocardial damage. Its clinical efficacy was related to its electrophysiologic properties and to two unique properties: its wide safety margin and its cumulative effect. The latter liberates patients from a rigid hourly schedule and provides for continuous antiarrhythmic control, days and even weeks after treatment is discontinued.

In a previous paper,[1] we reported the usefulness of amiodarone in controlling tachyarrhythmias associated with the Wolff-Parkinson-White syndrome. The drug was subsequently shown to have similar efficacy in a variety of atrial and ventricular arrhythmias. In this paper we present results obtained in 252 patients, including several with disabling or life-threatening arrhythmias or arrhythmias resistant to other antiarrhythmic agents. The properties of the drug underlying its clinical efficacy as well as side effects and contraindications are emphasized.

Material and Methods

Two hundred fifty-two patients with persistent or recurrent supraventricular or ventricular arrhythmias were studied. They were classified into six groups according to their primary arrhythmia (Tables I to VI). Ninety-eight patients had previously been treated unsuccessfully with various antiarrhythmic agents (Tables I, II, V and VI); in 154 patients, amiodarone was the first antiarrhythmic drug given. Each episode of arrhythmia was studied with long electrocardiographic tracings and, when needed for diagnostic purposes, atrial electrograms (22 cases), His bundle electrograms (6 cases), atrial pacing (6 cases) and ventricular pacing (8 cases).

*Amiodarone** is a benzofuran derivative that shares some structural similarities with thyroxine (Fig. 1). The pharmacologic effects have been summarized in previous papers.[2,3] Essentially, amiodarone increases coronary blood flow, reduces myocardial oxygen consumption without significantly affecting cardiac output, causes an atropine-resistant bradycardia and antagonizes the effects of catecholamines and sympathetic stimulation without causing competitive beta adrenergic receptor blockade.[2]

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*Amiodarone (generic name) was kindly supplied by Laboratorios Roemmers, Buenos Aires, for this study, and was originally discovered and manufactured by Services de Recherche Labaz, Brussels.

TABLE I

Repetitive Atrial Flutter and Fibrillation: Treatment With Amiodarone in 30 Cases

Diagnosis	Results With Amiodarone				Previous Treatment													
					Q		D		βB		Proc		A		L		DPH	
	Cases (no.)	E	G	P	Cases (no.)	G	P	G	P	G	P	G	P	G	P	G	P	G	P
Wolff-Parkinson-White syndrome	7	7	···	···	6	1	5	···	2	···	2	···	···	···	1	···	1	···	1
No heart disease	6	6	···	···	4	···	3	···	1	···	1	···	···	···	···	···	···	···	···
Arterial hypertension	5	4	···	1	5	···	3	1	3	···	2	···	···	···	···	···	···	···	···
Coronary insufficiency plus arterial hypertension	4	4	···	···	1	···	···	···	1	···	···	···	···	···	···	···	···	···	···
Mitral insufficiency	1	1	···	···	1	···	···	1	···	···	···	···	···	···	···	···	···	···	···
Chronic Chagasic myocarditis	1	1	···	···	1	···	1	···	1	···	···	···	···	···	···	···	···	···	···
Pulmonary embolism	1	1	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···
Chronic hiatus hernia	1	1	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···
Chronic bronchitis	1	1	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···	···
Hypothyroidism	1	1	···	···	1	···	1	···	···	···	···	···	···	···	···	···	···	···	···
Diabetes	1	1	···	···	1	···	1	···	1	···	···	···	1	···	···	···	···	···	···
Undetermined	1	1	···	···	1	···	1	···	1	···	1	···	···	···	···	···	···	···	···
Total	30	29	···	1	21														

A = ajmaline; βB = beta blocking agents; D = digitalis; DPH = diphenylhydantoin; E = excellent; G = good; L = lidocaine; P = poor; Proc = procainamide; Q = quinidine.

TABLE II

Repetitive Supraventricular Tachycardia: Treatment With Amiodarone in 59 Cases

Diagnosis	Results With Amiodarone				Previous Treatment								
					Q		D		βB		Proc		
	Cases (no.)	E	G	P	Cases (no.)	G	P	G	P	G	P	G	P
Wolff-Parkinson-White syndrome	20	20	···	···	13	1	9	1	3	1	6	···	2
Lown-Ganong-Levine syndrome	3	3	···	···	2	1	1	···	1	···	1	···	1
Cardiomyopathy	5	4	···	1	2	···	···	···	1	···	1	···	···
Chronic Chagasic myocarditis	1	1	···	···	···	···	···	···	···	···	···	···	···
Coronary insufficiency	4	4	···	···	2	···	1	···	···	···	1	···	···
Arterial hypertension	5	5	···	···	1	···	···	···	1	···	···	···	···
Valvular heart disease	2	1	1	···	1	···	···	···	1	···	···	···	···
No heart disease	16	16	···	···	8	···	4	···	2	2	5	···	···
Undetermined	3	3	···	···	3	···	2	···	2	···	2	···	···
Total	59	57	1	1	32								

βB = beta blocking agents; D = digitalis; E = excellent; G = good; P = poor; Proc = procainamide; Q = quinidine.

TABLE III

Atrial Extrasystoles: Treatment With Amiodarone in 10 Cases

Diagnosis	Results With Amiodarone			
	Cases (no.)	E	G	P
No heart disease	3	3	···	···
Severe arterial hypertension	3	2	···	1
Coronary insufficiency plus arterial hypertension	1	1	···	···
Mild arterial hypertension plus chronic hiatus hernia	1	···	1	···
Diabetes	1	···	···	1
Coronary insufficiency	1	1	···	···
Total	10	7	1	2

E = excellent; G = good; P = poor.

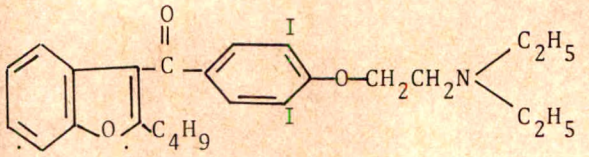
TABLE IV

Miscellaneous Arrhythmias: Treatment With Amiodarone in Eight Cases

Diagnosis	Arrhythmia	Results With Amiodarone			
		Cases (no.)	E	G	P
Undetermined	Chronic atrial flutter	1	···	···	1
Arterial hypertension	Chronic atrial tachycardia with A-V Wenckebach block	1	1	···	···
Undetermined	Junctional rhythm with Wenckebach exit block	1	···	1	···
Chronic Chagasic myocarditis	Chronic atrial fibrillation with high ventricular response	1	1	···	···
Undetermined	Sinus tachycardia	4	4	···	···
Total		8	6	1	1

A-V = atrioventricular; E = excellent; G = good; P = poor.

AMIODARONE



2-butyl, 3-(4, diethylaminoethoxy, 3 , 5'-diiodo, benzoil)benzofuran hydrochloride.

FIGURE 1. Structural formula of amiodarone.

Treatment protocol: Amiodarone was administered orally in a dose of 200 (one tablet) to 800 mg/day, in a single or divided dose according to patient preference. The most common initial dose was 600 mg/day; when the desired antiarrhythmic effect was obtained, usually after 4 to 8 days of treatment, the dose was reduced to the minimum that would keep the patient free of arrhythmia, generally 200 to 400 mg/day. Treatment and follow-up periods ranged from 15 days to 3 years (average of 17 months). In 53 patients, administration of amiodarone was discontinued for 2 days every week or 1 week every month to assess whether this interruption of treatment was compatible with continuous control of the arrhythmia. In eight patients with daily episodes of supraventricular tachycardia, treatment was deliberately interrupted (and reinstituted) several times in order to evaluate the persistence of the an-

TABLE V

Persistent Ventricular Extrasystoles: Treatment With Amiodarone in 101 Cases

Diagnosis	Results With Amiodarone				Previous Treatment											
					Q		D		βB		Proc		L		DPH	
	Cases (no.)	E	G	P	Cases (no.)	G	P	G	P	G	P	G	P	G	P	G	P
Chronic Chagasic myocarditis	24	21	1	2	6	...	...	...	1	...	2	...	3	1	1	1	2
No heart disease	17	12	...	5	7	...	5	...	1	...	1	...	3	1	...	...	...
Cardiomyopathy	13	12	1	...	1	...	...	...	...	...	1	...	...	...	...	...	...
Coronary insufficiency	19	17	2	...	3	...	1	...	1	...	2	...	1	...	1	...	...
Acute myocardial infarction	4	4	...	...	1	...	...	...	...	...	...	...	1	...	1	...	...
Postmyocardial infarction ventricular aneurysm	3	3	...	...	1	...	1	...	...	...	...	...	1	...	...	...	...
Arterial hypertension	8	7	...	1	2	...	1	...	1	...	1	...	...	...	...	...	...
Hyperthyroidism	4	2	1	1	...	...	...	...	...	...	...	...	...	...	...	...	...
Chronic cor pulmonale	3	3	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Diabetes	1	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Posterior mitral leaflet dysfunction	1	...	...	1	...	...	...	...	...	...	...	...	...	...	...	...	...
Mitral-aortic disease	1	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Undetermined	2	1	...	1	...	...	...	...	...	...	...	...	...	...	...	...	...
Thyroid adenoma with normal function	1	1	...	...	1	...	...	...	...	...	1	...	1	...	...	...	1
Total	101	85	5	11	22												

βB = beta blocking agents; D = digitalis; DPH = diphenylhydantoin; E = excellent; G = good; L = lidocaine; P = poor; Proc = procainamide; Q = quinidine.

TABLE VI

Repetitive Ventricular Tachycardia: Treatment With Amiodarone in 44 Cases

Diagnosis	Results With Amiodarone				Previous Treatment											
					Q		D		βB		Proc		L		DPH	
	Cases (no.)	E	G	P	Cases (no.)	G	P	G	P	G	P	G	P	G	P	G	P
Postmyocardial infarction ventricular aneurysm	8 (6*)	6 (5*)	...	2 (1*)	6	...	5	...	1	...	1	...	6	...	6	...	4
Chronic Chagasic myocarditis	14	12	2	...	6	...	1	...	2	...	...	...	2	2	2	...	1
Cardiomyopathy	7	6	...	1	3	...	...	1	1	...	1	...	1	1	1	...	...
Hypertensive heart disease	5	2	2	1	1	...	...	...	1	...	...	...	1	...	...	...	...
Acute myocardial infarction	3	3	...	...	2	...	1	...	...	...	...	...	1	1	...	...	...
Coronary insufficiency plus arterial hypertension	2	1	...	1	2	...	1	...	2	...	1	...	...	1	1	1	...
Diabetes and gall bladder disease	1	1	...	...	1	...	...	...	...	...	...	...	1	...	...	...	...
Chronic renal insufficiency	1	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Mitral-aortic disease with complete A-V block	1 (1*)	1 (1*)	...	...	1	...	...	...	...	...	...	...	...	...	1	...	...
Hypothyroidism	1	1	...	...	1	...	1	...	1	...	1	...	1	...	...	...	1
Undetermined	1	...	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Total	44 (7*)	34 (6*)	5	5 (1*)	23												

*Patients with repetitive ventricular fibrillation. βB = beta blocking agents; D = digitalis; DPH = diphenylhydantoin; E = excellent; G = good; L = lidocaine; P = poor; Proc = procainamide; Q = quinidine.

tiarrhythmic effect. Findings in these patients were compared with data obtained from similar analyses in eight patients who discontinued treatment spontaneously.

Forty-two patients presenting the most severe arrhythmias with or without atrioventricular (A-V) or intraventricular block were continuously monitored in the intensive care unit during the first days. The remaining patients were treated on an ambulatory basis. In 17 patients with advanced A-V or intraventricular block, treatment with amiodarone was started only after implantation of a temporary demand pacemaker. This served both to prevent possible complications and to permit study of the effects of the drug under such conditions. In 51 patients with isolated bundle branch block, the drug was administered without previous insertion of a pacemaker. In 25 patients with life-threatening arrhythmias, the treatment was started simultaneously with the administration of an antiarrhythmic drug of rapid action (Table VII); use of the latter was interrupted when the arrhythmia was controlled with amiodarone. In 47 patients an attempt was made to correlate at weekly intervals the antiarrhythmic action with the changes in ventricular repolarization caused by the drug, and with the presence of corneal microdeposits, observed through a slit-lamp microscope.

Grading of therapeutic response: Response to the administration of amiodarone was classified as excellent, good or poor, according to whether the drug caused, respectively, total suppression of the arrhythmia, a reduction of 50 percent or more in frequency of occurrence of arrhythmia or a reduction of less than 50 percent. However, the evaluation varied according to whether the patients had repetitive tachyarrhythmias or persistent extrasystoles. Since almost all episodes of paroxysmal tachyarrhythmia were clearly symptomatic, total suppression in these cases was judged present when the patient stated that the episodes had ended, and this judgment was verified in the group of patients treated and monitored in the intensive care unit. To quantitate the effect, the total number of tachyarrhythmic episodes occurring the month before and after administration of the drug were counted and compared. By contrast, because continuous electrocardiographic tape recording was unavailable, and because patients with persistent extrasystoles were commonly unaware of the arrhythmia, these patients were accepted for entry into the study only when all tracings of 5 minutes' duration recorded at weekly intervals for 4 weeks showed at least 10 extrasystoles/min. The effect of the drug was judged excellent when no extrasystole occurred in four similar weekly tracings recorded the month after initiation of treatment, good when the total number of extrasystoles similarly counted decreased by more than 50 percent and poor when the number was reduced by less than 50 percent.

Results

Supraventricular Arrhythmias

Supraventricular arrhythmias showed the greatest sensitivity to the drug. Thus, these arrhythmias were totally suppressed in 98 of 106 patients (92.4 percent), only 5 patients (4.7 percent) showing a poor response to amiodarone. The drug's efficacy was even more remarkable in the following subgroups. Recurrent paroxysmal atrial flutter or fibrillation was totally suppressed in 29 of 30 patients (96.6 percent) (Table I). During the month preceding treatment, 24 of these 30 patients had 720 episodes of tachyarrhythmia (average 30 episodes, range 2 to 140), and the other 6 had continuously recurring short and uncounted episodes. In the 29 successful cases, the total incidence was reduced to 0 during the month after the initial 4 to 8 day period of treatment. Total suppression occurred also in 57 of 59 patients with repetitive supraventricular tachycardia (Table II). In the month before treatment, 54 of these 59 patients had 965 episodes of tachyarrhythmia (average 17.8 episodes, range 1 to 80), and the other 5 had continuously recurring and uncounted episodes. Total suppression occurred in all 27 patients (100 percent) with tachyarrhythmias related to the Wolff-Parkinson-White syndrome (Tables I and II). In the month before treatment, 25 of these 27 patients had 351 episodes (average 14, range 1 to 60), and the other 2 had continuously recurring episodes. In 19 of these 27 cases, amiodarone blocked anterograde conduction in the anomalous bundle, causing normalization of the QRS complex. The 89 patients in these three groups had had paroxysmal arrhythmia for 1 to 53 years (average 12 years); 13 patients had had the arrhythmia for at least 5 years, and 34 for at least 10 years. However, complete control of the arrhythmia was maintained during the entire follow-up period (1 to 36 months, average 16 months), provided that the correct dosage of the drug was also maintained. Amiodarone was less effective in treatment of simple atrial extrasystoles (Table III).

Ventricular Arrhythmias

Amiodarone produced excellent results in 119 of 145 patients (82.0 percent) with ventricular arrhythmias and poor results in only 16 (11.0 percent) (Tables V and VI). It was in this group that the drug proved most valuable, because it included the sickest patients with the most dangerous arrhythmias. Thus, amiodarone caused total suppression and control of recurrent ventricular tachycardia in 34 of 44 patients (77.2 percent) who had responded poorly to previous treatment with other drugs at usual therapeutic doses (Table VI). Of these 44 patients, 32 had continuously recurring episodes of ventricular tachycardia during the week before treatment, and the other 12 had 274 episodes (average 22.8, range 4 to 30) during the month before administration of amiodarone. Special mention must be made of the excellent results obtained in six of eight patients with repetitive ventricular tachycardia related to a postmyocardial infarction ventricular aneurysm and in six cases associated with recurrent ventricular fibrillation. Despite the administration of lidocaine and other drugs (Cases 1 to 7, Table VII), seven of the eight patients required repeated electric cardioversion to permit survival until amiodarone could provide total control of the arrhythmia. Two of these eight patients (Cases 1 and 5, Table VII) underwent surgical resection of the aneurysm but had no reduction in episodes of ventricular tachycardia or fibrillation postoperatively. Of the six survivors at the time of discharge, 1 died suddenly 2 months later, 15 days after abandoning treatment; another died 18 months later of mediastinal carcinoma. The other four are free of arrhythmia and doing well after 18 to 26 months (average 23 months) of follow-up study.

TABLE VII

Combined Treatment in Dangerous Arrhythmias in 25 Cases

Case no.	Arrhythmia	Clinical Status and Diagnosis	Drugs Initially Used With Amiodarone						Other Procedures		Days Required for Total Control of Arrhythmia	Follow-up
			L	Q	Proc	DPH	βB	D	Cardioversion	OD		
1	Repetitive VT and VF	Cardiogenic shock‡; postinfarction ventricular aneurysm	—	—	—	—	—	—	+ (in 50 instances)	+—	4	2 years, alive
2	Repetitive VT	CHF; cardiogenic shock‡; postinfarction ventricular aneurysm	—	—	—	...	...	...	+ (in 15 instances)	—	...	56 days§ (cardiogenic shock)
3	Repetitive VT and VF	CHF; postinfarction ventricular aneurysm	+	—	—	...	...	—	+ (in 6 instances)	...	4	18 months, alive
4	Repetitive VT and VF	Postinfarction ventricular aneurysm	—	—	—	...	...	...	+ (in 5 instances)	—	3	18 months§ (mediastinal carcinoma)
5	Repetitive VT and VF	Cardiogenic shock‡; postinfarction ventricular aneurysm	—	—	—	—	...	...	+ (in 21 instances)	—	...	§(1 day after aneurysmectomy)
6	Repetitive VT and VF	Cardiogenic shock‡; postinfarction ventricular aneurysm	—	...	...	—	...	...	+ (in 3 instances)	...	3	2 years, alive
7	VT, VFI, VF	Postinfarction ventricular aneurysm; diabetic acidosis; septic shock	+	—	...	...	...	...	+ (in 8 instances)	...	7	2 months§ (SCD 15 days after discontinuing treatment)
8	Repetitive VT	Cardiomegaly +++; old posterior infarction; AH	+	...	...	...	...	...	...	...	5	15 days§ (SCD 8 days after discontinuing treatment)
9	VT, VE	Old anterior and posterior myocardial infarction; postinfarction angina	—	...	...	...	...	...	+ (in 4 instances)	...	4	14 months, alive
10	Repetitive VT; multifocal VE	AH; old anterolateral myocardial infarction; repetitive pulmonary and systemic embolism	+	...	—	...	...	...	...	...	5	2 years, alive
11	Multifocal VE	CHF; cardiomegaly ++++; cardiomyopathy	+	...	...	...	...	...	...	...	4	1 year, alive
12	Multifocal VE; repetitive PAT, PAFI, PAF	Cardiomegaly ++; CHF; cardiomyopathy	+*	...	...	...	...	...	—	...	4†	15 days§ (massive pulmonary embolism) without arrhythmias
13	Multifocal VE	Cardiomegaly +++; CHF; cardiomyopathy	+	...	...	...	...	...	...	—	3	1 month, unknown
14	Repetitive VT	Complete A-V block; cardiogenic shock‡	+	...	...	...	...	...	...	—	7	2 months, unknown
15	Multifocal VE	Cardiomegaly ++++; complete A-V block; Ch.Myo	+	...	...	...	...	...	...	—	2	1 year, alive
16	VT; multifocal VE	CHF; cardiomegaly ++; Ch.Myo	+	...	—	...	...	...	...	...	2	1 year, alive
17	VT; multifocal VE	Cardiomegaly +++; Ch.Myo	+	...	...	...	...	...	...	...	10 (good); 45 (excellent)	17 months, alive
18	VT; multifocal VE	CHF; cardiomegaly +++; hepatic and renal insufficiency; Ch.Myo	+	...	...	...	...	...	...	...	4	12 days§ (hepatic and renal insufficiency) without arrhythmias
19	VT; multifocal VE	CHF; cardiomegaly ++++; hepatic and renal insufficiency; Ch.Myo	+	...	...	—	...	...	...	...	6	20 days§ (hepatic and renal insufficiency) without arrhythmias
20	VT; multifocal VE	CHF; cardiomegaly ++; Ch.Myo	+	...	...	...	...	...	...	...	7	18 months, alive
21	Repetitive VT and VF	Complete A-V block; mitral valvulopathy; AH	+	...	...	...	...	...	+	—	5	18 months, alive
22	Multifocal VE	Severe chronic cor pulmonale	+	...	...	...	...	...	...	...	3	2 months, unknown
23	Multifocal VE, PAF	Severe chronic cor pulmonale	+	...	...	...	...	...	...	...	3	15 months, alive
24	PAFI, PAF, VF	Cardiogenic shock‡; WPW syndrome	—	—	—	—	—	—	+	—	3	3 years, alive
25	PAFI	CHF; mitral insufficiency	—	—	—	—	—	—	+	—	3	6 months, alive

*Excellent result for ventricular extrasystoles only; †Excellent result for all the arrhythmias; ‡Cardiogenic shock was related to the arrhythmia; §Died; + = excellent result; — = poor result; ++ = moderate; +++ = severe; ++++ = extreme.

AH = arterial hypertension; A-V = atrioventricular; βB = beta blocking agents; CHF = congestive heart failure; Ch.Myo = chronic Chagasic myocarditis; D = digitalis; DPH = diphenylhydantoin; L = lidocaine; OD = overdrive pacing; PAF = paroxysmal atrial fibrillation; PAFI = paroxysmal atrial flutter; PAT = paroxysmal atrial tachycardia; Proc = procainamide; Q = quinidine; SCD = sudden cardiac death; VE = ventricular extrasystoles; VF = ventricular fibrillation; VFI = ventricular flutter; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White.

The results were also excellent in 12 of 14 patients with ventricular tachycardia related to Chagasic myocarditis, and in 6 of 7 patients with ventricular tachycardia related to chronic nonspecific cardiomyopathy (Table VI). Excellent results were obtained in the control of premature ventricular contractions in 21 of 24 patients with Chagasic myocarditis, in 24 of 26 cases of ischemic heart disease and in 85 of a total of 101 patients (84.1 percent) with ventricular extrasystoles (Table V). The efficacy was slightly less for ventricular extrasystoles occurring in patients with no detectable heart disease.

Serious life-threatening arrhythmias: Table VII summarizes the findings in a subset of 25 critically ill patients with serious arrhythmias who were given amiodarone together with other antiarrhythmic drugs of rapid action, particularly lidocaine, and who were treated with cardioversion and overdrive pacing to permit survival until amiodarone became effective in controlling the arrhythmia. Since in all such cases the arrhythmias were of recent onset or had been documented only at the time of admission, it is difficult to be certain that the excellent results were due to amiodarone and not to the other antiarrhythmic drugs and maneuvers, or to the natural course of the disease. However, previous experience with similar patients in our coronary care unit before the introduction of amiodarone, as well as the experience of others,[4–17] suggests that amiodarone played an important if not an essential role in providing total control of the arrhythmias after the first few days of treatment.

Persistence of Amiodarone Effect

In 53 patients with repetitive supraventricular arrhythmias (29 cases) or persistent extrasystoles (24 cases), discontinuation of administration of amiodarone for 2 days every week (47 cases) or 1 week every month (6 cases) revealed no evidence of recurrence of the arrhythmia. To assess with greater precision the persistence of the antiarrhythmic effect, treatment with amiodarone was deliberately interrupted several times and for variable periods in eight patients with daily episodes of supraventricular tachycardia. These patients were evaluated together with eight similar patients who had abandoned the treatment spontaneously and returned for consultation when the arrhythmia reappeared. Four of the 16 patients had taken 400 mg/day of amiodarone for 30 to 45 days. In this group the repetitive arrhythmias reappeared 10 to 20 days after interruption of treatment. In the other 12, who had been taking a similar dose for several months, the therapeutic effect was maintained for up to 30 days (9 cases) and even 45 days (3 cases) after discontinuation of amiodarone. When the tachyarrhythmias reappeared, the frequency of the episodes was initially much less, and it generally took an additional 10 to 15 days to reach the daily frequency documented before amiodarone was first administered.

Side Effects

Constipation and light skin rashes (photodermatosis) occurred in approximately 10 percent of the patients but were never a cause for discontinuing treatment. Only 2 of the 252 patients required interruption of treatment, one because of nausea and vomiting and one because of the occurrence of erythema nodosum.

Corneal microdeposits: These deposits were documented in all 47 patients who were examined for this condition. Although the magnitude and time of appearance were in general dose-dependent, in some patients the microdeposits were initially detected after 14 days and in others only after 4 months of treatment. Like other iodine compounds,[18] amiodarone is excreted through the lacrimal gland and is deposited directly or

TABLE VIII

Conduction Disturbances: Treatment With Amiodarone in 67 Cases

Type of Arrhythmia	Cases (no.)	Preexistent Conduction Disturbances	Effects on Conduction During Amiodarone Treatment
Paroxysmal atrial flutter and fibrillation	1	1° A-V block	...
	2	I RBBB	...
	1	I RBBB-LAH	...
	1	Intermittent RBBB	...
Paroxysmal supraventricular tachycardia	1	Intermittent RBBB-LPH	...
	1	I RBBB	...
	1	RBBB	...
	1	LAH	...
	2	Intermittent LBBB	...
	1	Intermittent LBBB-LAH	...
Atrial extrasystoles	2	RBBB	Higher degree of RBBB (1)
Miscellaneous	1	2° A-V block with Wenckebach periods	...
Ventricular extrasystoles	3	1° A-V block	...
	1	High degree A-V block	...
	1	Complete A-V block	...
	7	RBBB-LAH	...
	3	I RBBB-LAH	...
	4	I RBBB	RBBB (1); 2° A-V block, Mobitz II (1)
	4	RBBB	
	2	Intermittent RBBB	1° A-V block, permanent RBBB-LAH (1)
	4	LAH	...
	1	I LBBB-LAH	...
	1	I LBBB	...
Ventricular tachycardia	2	Complete A-V block	...
	1	High degree A-V block	...
	2	1° A-V block	...
	1	1° A-V block-LAH	...
	1	Intermittent RBBB-LAH	Permanent RBBB-LAH
	8	RBBB-LAH	...
	2	RBBB	...
	3	LAH	...
	1	I LBBB	...
	1	Intermittent RBBB	Permanent RBBB

Figures in parentheses indicate number of cases.

A-V = atrioventricular; I = incomplete; LAH = left anterior hemiblock; LBBB = left bundle branch block; LPH = left posterior hemiblock; RBBB = right bundle branch block.

as a metabolite in the most superficial layers of the cornea.[19–24] A mechanical factor plays a role, because the deposits occur initially and predominantly in the lower third of the cornea, along the line where the upper border of the inferior eyelid makes contact with the eye. Accordingly, they less frequently invade the pupillary area and seldom cause subjective phenomena. Only 6 of our 252 patients complained spontaneously of visual problems: blurred vision in 4 and colored vision in 2. It is well established that the corneal microdeposits are reversible[19,21–23] although complete disappearance may take several months. Microdeposits did not occur in any of 13 children, aged 8 months to 15 years, receiving amiodarone,[25] probably because of the greater secretion and faster circulation of the lacrimal fluid in children compared with adults. The microdeposits suggest that the drug may also be deposited in other body tissues.[23,26–29]

In 47 patients, the corneal microdeposits were correlated with therapeutic efficacy and with changes in ventricular repolarization (bifid or bimodal T waves, prominent U waves, prolonged Q-T interval) that commonly accompany the administration of amiodarone.[1,3,30] Although in many patients the three variables were dose-dependent and related to each other, the general correlation was poor. Thus, although some patients with overt changes in ventricular repolarization and dense microdeposits had a poor therapeutic response, others had an excellent antiarrhythmic effect accompanied by an insignificant amount of microdeposits and practically no change in ventricular repolarization.

Effects on conduction and automaticity: Amiodarone caused further deterioration of conduction in 6 (8.8 percent) of 68 patients with intraventricular or A-V block, or both (Table VIII). In general, this consisted of an increment in the degree of block in a previously damaged fascicle. However, no case of complete A-V block was provoked by the drug. In three patients with such A-V block, amiodarone did not change the rate of the spontaneous idioventricular rhythm; this finding is consistent with previous data[31] indicating that the drug does not significantly affect ventricular automaticity. Right bundle branch block developed in 2 (1.09 percent) of the 184 patients without conduction defects. However, both patients had shown right bundle

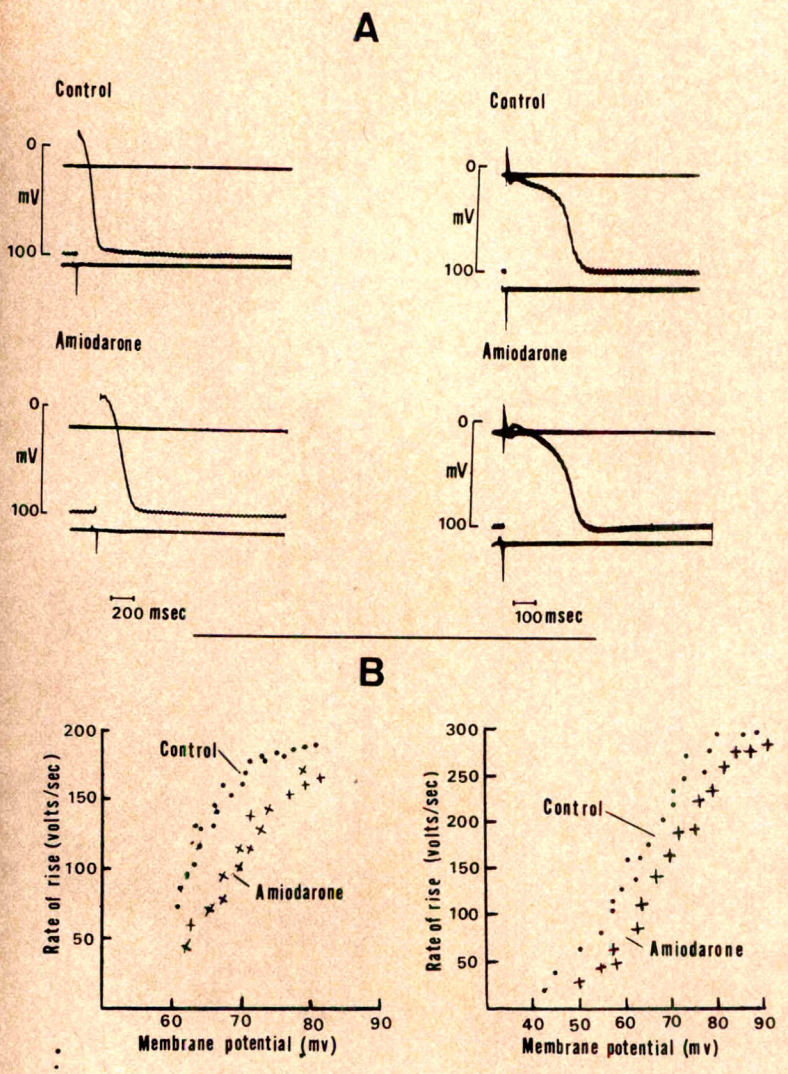


FIGURE 2. Electrophysiologic study of ventricular and Purkinje fibers of a rabbit heart, pretreated for 4 weeks with amiodarone, 100 mg/kg per day orally. **A, left,** transmembrane action potential and dV/dt recorded from a ventricular fiber from a control animal and from another one receiving amiodarone. Action potential duration is 57 and 60 percent greater at 50 percent and 90 percent repolarization, respectively, in the fiber of the animal pretreated with amiodarone. No significant difference occurs in the resting potential or in the amplitude of the action potential. **Right,** Purkinje fibers of the right bundle branch in the same two animals. A slight prolongation of the action potential duration (14 percent at 50 percent repolarization) is the only difference between the two fibers. **B, left,** depression of membrane responsiveness caused by amiodarone in a ventricular fiber. The curves were obtained by premature stimulation at different coupling intervals, delivered every 10 regular beats at a basic cycle length of 800 msec. **Right,** the depression of membrane responsiveness is similar but quantitatively less important in a Purkinje fiber explored at a basic cycle length of 1,000 msec. Data in **A** and **B** are representative of results obtained in 54 ventricular and 48 Purkinje fibers from 16 rabbit hearts, 8 pretreated with the same dose of amiodarone. Since amiodarone has no direct effect when added to the superfusant (standard Tyrode solution), the drug was administered in vivo, as indicated, and the control tissues were from tissue of nontreated animals. The control and pretreated tissues showed results similar to those illustrated when both were studied in the same bath preparation.

branch block spontaneously 5 to 12 months before, thus indicating that amiodarone only uncovered a latent conduction disturbance.[32]

Practically all the patients under prolonged treatment manifested sinoatrial slowing, which was dose-dependent and proportional to the spontaneous heart rate.[3,30,33] In most patients, the sinus rate was maintained at 55 to 75 beats/min. In 3 of the 252 patients amiodarone caused pronounced but still asymptomatic bradycardia (37 to 40 beats/min). The bradycardic action was useful in the treatment of sinus tachycardia. In four patients with pronounced and symptomatic sinus tachycardia (120 to 160 beats/min), the heart rate was slowed and stabilized below 80 beats/min after 6 to 10 days of treatment (Table IV). The drug was equally effective in 10 other patients with pronounced sinus tachycardia associated with other arrhythmias.

Thyroid function: A molecule of amiodarone contains 2 atoms of iodine,[1,3,26,34,35] and the administration of 400 mg (a common daily dose) is equivalent to 148.8 mg of iodine or 24 drops of Lugol solution. Because of this, amiodarone may uncover the existence of subclinical forms of both hypothyroidism and hyperthyroidism.[36–38] Symptomatic hypothyroidism developed in 2 of our 252 patients and symptomatic hyperthyroidism in 2 others.

Electrophysiologic Studies

Singh and Vaughan Williams[34] reported that amiodarone, administered intraperitoneally to rabbits in a dose of 20 mg/kg body weight daily for 6 weeks, caused a significant prolongation of the action potential duration in atrial and ventricular muscle without changes in the resting membrane potential and with a slight depressing effect on the maximal rate of depolarization. They therefore classified amiodarone as having a class III antidysrhythmic action,[39,40] which they attributed to prolongation of the action potential. Because no other electrophysiologic studies have been reported, we give here the following preliminary data from studies now under way in our laboratory: (1) amiodarone prolongs the action potential duration of atrial and ventricular fibers and to a lesser degree of Purkinje fibers of rabbit and canine hearts, without changing the resting potential (Fig. 2A). (2) It diminishes the maximal rate of rise of the action potential (Fig. 2A) and slows conduction velocity. (3) It depresses membrane responsiveness (Fig. 2B). (4) It does not significantly depress the spontaneous diastolic depolarization of Purkinje fibers. (5) It has a strong antifibrillatory action.

After ligation of the anterior descending coronary artery at its origin, amiodarone prevented the occurrence of ventricular fibrillation in all 10 pretreated dogs receiving orally 10 to 40 mg/kg daily for 1 to 4 weeks, whereas ventricular fibrillation occurred in 7 of 8 untreated animals. Five of the pretreated animals had no ventricular extrasystoles after ligation; four had isolated and transient ventricular extrasystoles 2.5 to 40 minutes after ligation, and brief episodes of transient ventricular tachycardia developed in one dog. By contrast, seven of the eight control dogs manifested multiple ventricular extrasystoles that rapidly degenerated into ventricular tachycardia and ventricular fibrillation 5 to 11 minutes after ligation.

Discussion

Antiarrhythmic Effects

Our results confirm previous data[25,31,41–43] indicating that amiodarone effectively controls, with minimal toxicity, atrial and ventricular arrhythmias in a variety of clinical conditions, including severe congestive heart failure and complicated forms of acute myocardial infarction. This efficacy was more readily demonstrated in a large series of patients with symptomatic repetitive tachyarrhythmias, who themselves clearly and uniformly reported total suppression of the episodes. Most such patients had had a long history of repetitive tachyarrhythmia which apparently concluded after treatment with amiodarone. Furthermore, in 16 patients with daily episodes of tachyarrhythmia, interruption

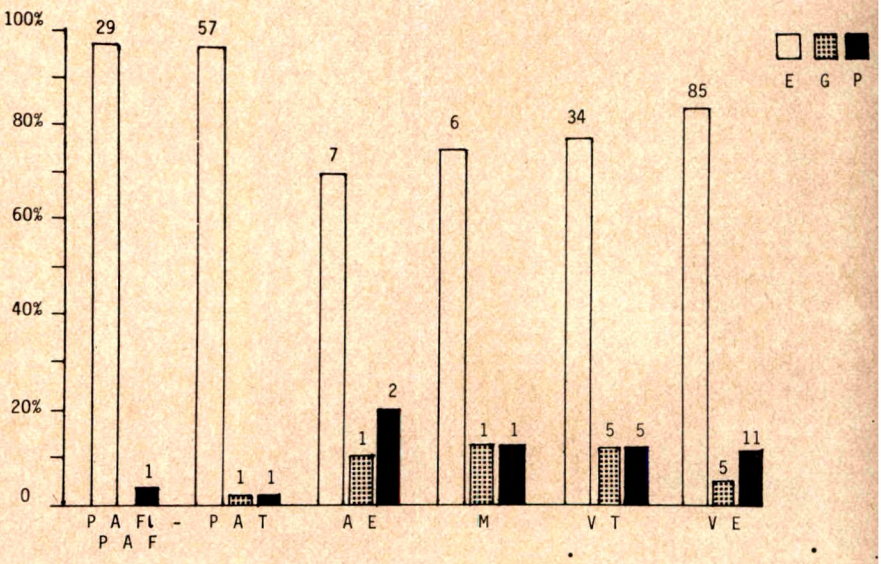


FIGURE 3. Comparative effects of amiodarone on different types of arrhythmias. Percent of results is indicated at left; numbers over bars indicate number of cases. **White bars** (E) = excellent results; **hatched bars** (G) = good results; **solid bars** (P) = poor results. AE = atrial extrasystoles; M = miscellaneous; PAF = paroxysmal atrial fibrillation; PAFl = paroxysmal atrial flutter; PAT = paroxysmal atrial tachycardia; VE = ventricular extrasystoles; VT = ventricular tachycardia.

of treatment was followed by recurrence of the arrhythmia after various periods of time, and reinstitution of treatment was again followed by total control of the arrhythmia. Becase continuous electrocardiographic tape recording was not utilized, it was more difficult to evaluate the effect of amiodarone in patients with persistent ventricular extrasystoles. Although we documented a remarkable reduction in the frequency of premature beats, we cannot be certain that total suppression was attained. However, our similar results in patients with both repetitive tachyarrhythmias and persistent extrasystoles (Fig. 3) suggest that the suppressive effect of the drug in patients with ventricular extrasystoles was at least highly significant.

Comparison with other antiarrhythmic drugs: It is difficult to establish valid comparisons of the efficacy of different antiarrhythmic drugs because criteria for selection of patients and evaluation of drug effects may vary according to the reported series. Nevertheless, the high percentage of excellent results shown in Figure 3 suggests that amiodarone compares favorably in therapeutic efficacy with quinidine,[5,44–48] procainamide,[5,44–46,49,50] lidocaine,[5,44,51–54] propranolol[5,44,55–57] and diphenylhydantoin[5,44,58–60] and appears to be superior to all of them in versatility, tolerance and simplicity of dose scheduling. A more direct comparison made among our own patients revealed that amiodarone provided total control and protection in 93 of 98 patients with recurrent disabling or dangerous supraventricular arrhythmias (53 cases) and ventricular arrhythmias (45 cases), whereas the other drugs mentioned, used singly or in different combinations, yielded only a poor response.

Ventricular arrhythmias related to postinfarction ventricular aneurysm: Postinfarction ventricular aneurysm may be accompanied by recurrent episodes of ventricular tachycardia and fibrillation, implying a bad or ominous prognosis. These episodes are extremely resistant to antiarrhythmic drugs,[10–17] and surgical resection of the aneurysm has been performed with various degrees of success.[10–17] Table VI shows that amiodarone provided total control in six of eight patients with such arrhythmias. Although there was no control group, the well known poor prognosis in similar cases[17] indicates that the drug played an important role in treatment. We have since learned that the initial administration of 1,000 to 1,500 mg/day of amiodarone may increase effectiveness of the drug and reduce to only 48 hours the time needed to develop its antiarrhythmic action.

Ventricular arrhythmias in chronic Chagasic myocarditis: Chagasic myocarditis causes frequent and multifocal ventricular premature beats,[4] which may degenerate into ventricular tachycardia or ventricular fibrillation, precipitating the sudden death commonly reported in this disease. Since these arrhythmias occur often in the presence of extensive intraventricular block, severe congestive heart failure and a greatly dilated heart, most antiarrhythmic drugs are ineffective and even dangerous. Therefore, it was surprising to us that amiodarone could be so effective and safe in treating ventricular extrasystoles and preventing the recurrence of ventricular tachycardia in patients with Chagasic myocarditis (Tables V and VI). Chagasic myocarditis can be taken as a clinical model providing possibly the most demanding conditions under which an antiarrhythmic drug can be tested. Two reasons may account for the unexpected efficacy and safeness of amiodarone under such unfavorable conditions: the lack of a significant negative inotropic effect and the potent antifibrillatory action.

Tachyarrhythmias associated with the Wolff-Parkinson-White syndrome: In a previous report,[1] we have shown the usefulness of amiodarone in controlling the tachyarrhythmias associated with the Wolff-Parkinson-White syndrome in 11 patients, and compared its effect with that of other drugs. Our experience has now been extended to 27 such patients and has again shown a 100 percent rate of efficacy (Tables I and II). No matter how favorable the surgical results may be,[6–9] our results show that surgery is unnecessary when amiodarone can be administered to patients with this condition.

Properties of Amiodarone

Three main properties appear to determine the usefulness of amiodarone as an antiarrhythmic agent: (1) electrophysiologic properties; (2) the drug's capacity for storage in the body and its cumulative effect; and (3) the lack of significant toxicity, which allows a wide margin of therapeutic dosage. Which electrophysiologic property is mainly responsible for the antiarrhythmic effect will probably be open to debate for some time. However, because many other drugs with comparable, different or even opposite electrophysiologic properties are also potent antiarrhythmic agents but less successful clinically, we believe that the electrophysiologic properties may be less decisive for the clinical effectiveness of amiodarone than the other properties to be discussed.

The cumulative effect: Amiodarone is variably absorbed from the intestinal tract and is well retained by the body, with a very slow rate of elimination.[26] Except for digitalis, most antiarrhythmic drugs now used are rapidly metabolized and excreted, have a short half-life, have a brief or ephemeral effect and must be administered at regular brief intervals. None of this is true of amiodarone. Although the half-life of the drug is still undetermined, it has been estimated that 30 days after its administration is discontinued the body concentration has diminished by only 16 to 34 percent.[26]

In 67 of our patients who had daily arrhythmias, amiodarone, at a dose of 400 to 600 mg/day, took 4 to 8 days to attain its therapeutic effect. When in 16 of these patients the administration of the drug was interrupted, it took a much longer time for the effect to disappear, and this interval was dose-dependent and related to the total time of previous treatment. Persistence of the antiarrhythmic effect for 10 to 20 days and even up to 30 and 45 days was not uncommon, and this long-term effect coincided with a similarly prolonged persistence of the electrocardiographic changes caused by the drug,[3] and with a prolonged persistence of the corneal microdeposits. Whatever the mechanism, this property con-

tributes greatly to the clinicial usefulness of amiodarone because it liberates patients from submission to a rigid hourly schedule and provides them with an apparently more continuous and sustained antiarrhythmic protection than is afforded by other drugs. It is worth mentioning that the electrophysiologic properties can be studied for many hours even though the Tyrode solution bathing the tissue (of pretreated animals) contains no drug, thus suggesting that amiodarone may be firmly bound to some receptor in the myocardial cells from which it dissociates only at a very slow rate. This may preclude the wide fluctuations in the tissue levels of the drug that characterize other antiarrhythmic drugs.[5,18,52,59]

The wide safety margin: Most antiarrhythmic drugs have a rather narrow therapeutic ratio (relation between the lethal [LD_{50}] and therapeutic dose)[18]; and classic drugs like quinidine and procainamide may kill by provoking ventricular fibrillation, even at therapeutic doses, if administered to patients with a severely damaged heart. Whereas the LD_{50} of quinidine and procainamide is approximately 2.5 times the therapeutic dose,[61,62] the LD_{50} of amiodarone is more than 10 times the therapeutic dose when the drug is given intravenously,[63] and there is practically no lethal dose when it is administered orally.[63] In practical terms, this means that it is impossible to kill an animal with an acute dose of orally administered amiodarone. In addition, the absence of other significant toxic effects explains the great safety with which amiodarone can be given to patients in large doses for long periods of time. This wide safety margin is at least partially related to the antifibrillatory action of the drug. From our clinical and experimental experience, it appears that ventricular fibrillation is unlikely to occur in the presence of sufficient premedication with amiodarone.

From experimental studies on the canine heart, it appears that amiodarone has little negative inotropic effect.[64] In this respect, our clinical study was even more reassuring. The response of patients with severe congestive heart failure clearly indicated that amiodarone lacked any significant negative inotropic effect.

Side Effects and Contraindications

The most important undesirable effect of amiodarone is the occurrence of corneal microdeposits. However, these deposits seldom cause ocular symptoms, are totally reversible and can be diminished or prevented by the use of eyedrops containing metilcelulose[37] or sodium-iodine heparinate.[19,37] The most relevant question concerning them is whether they can cause irreversible damage although this has never been reported. The widespread European use of amiodarone as an antianginal agent for 10 years[19,21,26,30,35,65] and the absence of reported late ill effects on the eye allow us to be optimistic, but every effort should be made to settle this point conclusively.

The most important contraindication is the presence of intraventricular or A-V block, a contraindication shared with other antiarrhythmic drugs such as quinidine,[44–48] procainamide[44,49,50] and even lidocaine.[32,51] Because amiodarone does not appear to depress ventricular automaticity as do the other drugs, its use is apparently safer. However, any one of these drugs, when greatly needed, can be given to patients with conduction disturbances, provided a temporary artificial pacemaker is inserted.

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Spectrum of Coronary Arterial Spasm. Clinical, Angiographic and Myocardial Metabolic Experience in 29 Cases

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A relationship of coronary arterial spasm to variant angina pectoris, subendocardial ischemia, major ventricular arrhythmias and myocardial infarction has been demonstrated. In 29 patients, spasm was angiographically observed in normal-appearing coronary arteries (7 patients) as well as superimposed on various degrees of coronary atherosclerotic obstruction (22 patients). All patients experienced an atypical anginal syndrome; 16 patients also experienced typical exertional angina. Coronary spasm appeared to be a major contributory factor in eight occurrences of myocardial infarction and in 11 incidents of ventricular tachycardia, ventricular fibrillation and heart block.

Coronary spasm in the 29 cases was distributed in the following fashion: left main trunk, 6 cases; right main trunk, 12 cases; proximal left anterior descending artery, 13 cases; proximal circumflex artery, 1 case; distal left anterior descending artery, 1 case; and distal circumflex artery, 2 cases. In 5 cases coronary spasm was noted at multiple sites.

In contrast to findings in patients manifesting only typical exertional angina, the hemodynamic findings during spasm were those of a hypodynamic state. Left ventricular systolic pressure decreased from 138.9 ± 6.0 (mean ± standard error of the mean) to 113.2 ± 6.2 mm Hg; left ventricular end-diastolic pressure did not change significantly. Myocardial lactate extraction during spasm was invariably markedly reduced: −53.19 percent ± 15.44 ($P < 0.001$). However, the effect of coronary sinus pacing on myocardial lactate extraction was not significantly abnormal: +15.74 percent ± 6.66.

The respective roles of medical and surgical intervention are uncertain. Only 3 patients had a completely satisfactory pharmacologic response to nitrates alone or in combination with propranolol, and the condition of 5 others was partially improved; the remaining 21 patients were judged intractable to medical management. Coronary bypass surgery was performed as the ultimate recourse in 18 patients. However, short-term results reveal that only nine (50 percent) showed improvement, four (22 percent) had myocardial infarction during or after surgery and four (22 percent) died.

These studies confirm that coronary arterial spasm is a definite pathogenetic factor in a variety of acute myocardial ischemic syndromes. The incidence and full clinical significance of this functional disorder remain to be determined.

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For nearly 100 years speculation has waxed and waned regarding the importance of coronary arterial spasm as a pathogenetic factor in acute myocardial ischemia.[1,2] With the recognition of a variant, nonexertional form of angina by Prinzmetal et al.,[3] coronary spasm has once again surfaced as a probable pathogenetic factor. In most cases of variant angina studied anatomically or arteriographically, a focal stenotic lesion of a major coronary artery corresponding to the site of electrocardiographic injury has been demonstrated.[4,5] Recently, Oliva et al.[6] showed

clear arteriographic documentation that spontaneously occurring coronary arterial spasm repeatedly accompanied Prinzmetal's variant angina. Furthermore, their studies showed the coronary arteries to be entirely free of obstruction during intervals between attacks. Similarly, Gianelly et al.[7] have demonstrated variant angina with only minimal coronary atherosclerosis. Hence, it is becoming increasingly evident that coronary arterial spasm is an important, if not predominant, factor in Prinzmetal's variant angina.

This study comprises 29 cases in which coronary spasm was documented. In addition to Prinzmetal's variant angina, a relation of coronary spasm to other myocardial ischemic syndromes has been found. The report provides a preliminary picture of the clinical, angiographic and myocardial metabolic findings in coronary arterial spasm.

Materials and Methods

Twenty-nine patients, 9 women and 20 men, aged 40 to 70 years, were hospitalized because of symptoms considered to represent either "intractable" angina pectoris, "unstable" angina pectoris or evolving myocardial infarction. All patients were studied with selective coronary arteriography using the Sones technique.[8] No premedication, including sedatives and tranquilizers, were given for at least 8 hours before study. Initially, all coronary arteriograms were performed without prior coronary vasodilator administration. Nitroglycerin was given sublingually only after completion of an initial series of coronary angiograms. When clinically feasible, coronary visualization was attempted during spontaneous chest pain. Since, in most cases, chest pain developed after the initial coronary injection, repeat coronary arteriograms were often performed before nitrates were administered sublingually. No attempt was made in any case to induce spasm artificially with pharmacologic or mechanical stimuli. Each coronary angiogram was performed with selective injection of 6 ml of meglumine diatrizoate and sodium diatrizoate (Renografin®-76).

Coronary arterial spasm was considered documented when the coronary segment was reduced in caliber, changed its configuration or demonstrated total obstruction in comparison with its initial or subsequent angiographic appearance. Prompt reversal of the narrowing usually, although not invariably, followed nitrate administration. Catheter-induced spasm could not be eliminated from consideration since some obstructions were located within 1 to 2 cm of the coronary ostium. However, cases in which coronary spasm was in close proximity to the catheter tip were included only if electrocardiographic abnormalities corresponding to the site of spastic obstruction were present before, during or after coronary angiography.

Coronary sinus blood was sampled in 15 cases after catheterization with a no. 7F Gorlin bipolar pacing catheter (USCI, Glens Falls, N. Y.). Blood was withdrawn from the coronary sinus and arterial circulation at rest, during coronary sinus

TABLE I

Clinical Features of 29 Cases

Case no.	Age (yr) & Sex	Percent Coronary Arterial Obstruction									Coll	Clinical comment
		L Main	R Main	LAD_p	$Circ_p$	L Marg	L Diag	LAD_d	R_d	$Circ_d$		
1	53M	...	0→40	80→90	...	...	75	...	60	...	No	Surg, I
2	46M	...	100	90→100	...	60	...	...	...	...	No	Surg, MI
3	53M	...	30	75→100	40	...	...	...	...	...	Yes	Surg, I
4	60M	90→100	...	...	...	...	...	...	40	...	No	Surg, +
5	49M	...	100	90→100	35	...	...	...	...	...	No	Surg, Pz, MI
6	46M	...	...	20→60	...	...	60	...	...	...	Yes	I
7	60M	...	0→100	...	...	...	...	...	...	...	No	A
8	47M	...	0→90	...	...	...	...	...	...	...	No	Pz, I
9	70F	...	50→70	...	...	70	...	50	...	...	No	Surg, I
10	55M	...	90	50→90	...	...	...	...	...	90	No	Surg, MI
11	61M	50→90	0→30	90	...	90	90	...	90	...	No	Surg, I
12	43F	...	0→50	0→90	0→20	...	...	...	...	...	No	Pz, I
13	51M	75→90	...	...	...	...	...	...	...	...	No	Surg, Pz, I
14	42M	...	...	90→100	...	...	...	...	...	...	No	Surg, A
15	66M	...	...	90→100	...	...	...	...	...	...	No	Surg, Pz, MI
16	48M	...	...	25→75	...	...	...	...	...	...	No	Surg, +
17	67F	...	0→100	...	...	...	...	...	...	...	No	Pz, MI, +
18	46M	80→95	...	...	...	...	...	...	...	...	No	Surg, +
19	45F	0→90	...	...	...	...	...	...	...	...	No	Surg, +
20	49F	...	0→90	...	...	...	...	...	...	...	No	Pz, A
21	45M	...	...	75→95	...	...	...	...	...	...	No	Surg, I
22	69M	...	...	20→90	...	...	...	...	...	...	No	Surg, I
23	53M	...	...	95	...	...	...	...	...	0→80	No	Surg, Pz, I
24	47F	...	75→95	50	50	...	...	...	...	...	No	Pz, A
25	53M	20→100	...	75	...	...	...	...	...	...	No	Surg, I
26	40F	...	...	10→90	...	...	...	...	...	...	No	A
27	49F	...	0→50	...	...	...	...	0→50	...	...	No	A
28	52F	...	0→75	...	...	...	...	...	...	30→95	No	Pz, MI
29	59M	...	50→90	...	...	...	...	...	...	...	No	A

A = angina recurred despite therapy; $Circ_d$ = circumflex artery (distal); $Circ_p$ = circumflex artery (proximal); Coll = collaterals; I = clinical improvement; LAD_d = left anterior descending artery (distal); LAD_p = left anterior descending artery (proximal); L diag = left diagonal artery; L main = left main stem; L Marg = left marginal artery; MI = myocardial infarction; Pz = Prinzmetal angina; R Main = right main stem; R_d = right coronary artery (distal); surg = surgical treatment; + = died; → = spastic change.

pacing at 140 beats/min. for 5 minutes and in the immediate postpacing interval. In addition, samples were obtained whenever chest pain or electrocardiographic ischemic injury developed spontaneously. Blood lactate concentrations were analyzed according to the Antonis method.[9] Percent of myocardial lactate extraction was calculated as:

$$\left(\frac{\text{arterial lactate concentration} - \text{coronary sinus lactate concentration}}{\text{arterial lactate concentration}}\right) \times 100.$$

The normal range of myocardial lactate extraction value for this laboratory is from 14.4 to 45.0 percent (mean ± standard error of the mean 19.9 percent ± 3.0).

Results

Clinical features: All patients had atypical anginal distress ranging in duration from 1 day to 4 years. In 19 cases the pain was sustained for 30 minutes or more, suggesting unstable angina or acute myocardial infarction. Eleven patients described the chest pain as occasionally fleeting in nature. Three patients experienced the discomfort as sharp (somatic in nature) rather than visceral in character. However, despite atypical features, 16 patients also experienced typical exertional angina pectoris. These latter patients had S-T segment abnormalities (more than 1 mm depression) in postexercise electrocardiograms. In patients manifesting only atypical angina pectoris, 3 of 13 had an abnormal postexercise electrocardiographic response.

Fifteen of the 29 patients had a history of one or more hospitalizations for acute myocardial infarction; however, only 6 had definitive QRS abnormalities in support of a diagnosis of prior myocardial infarction. In each of these cases coronary spasm was found to correspond with the site of infarction.

During spontaneous nonexertional angina, electrocardiograms showed abnormalities of the S-T segment or T wave in all cases. An epicardial current injury was observed in nine. The remaining 20 showed significant S-T depression or coved T wave inversion. Cardiac arrhythmias were common. Ten patients had frequent (5 or more/min) premature ventricular contractions. Ventricular tachycardia or ventricular fibrillation, or both, was observed in seven. Second and third degree heart block occurred in four.

Hemodynamic findings: Systolic arterial pressure (138.9 ± 6.0 mm Hg) and left ventricular end-diastolic pressure (10.8 ± 1.7 mm Hg) were normal under control conditions. However, during chest pain systolic pressure decreased (113.2 ± 6.2 mm Hg) ($P < 0.05$) while left ventricular end-diastolic pressure (14.5 ± 2.8 mm Hg) did not alter significantly. Only six patients had an increased left ventricular end-diastolic pressure when chest pain developed. No significant change in heart rate occurred despite chest pain (71.8 ± 2.8 beats/min without pain versus 73.1 ± 1.9 beats/min with pain).

Angiographic findings (Tables I and II): Coronary spasm, as defined arteriographically, was distributed among the 29 patients as follows: left main trunk, 20 percent (6 of 29); right main trunk, 41.4 percent (12 of 29); proximal left anterior descending artery, 44 percent (13 of 29); proximal circumflex artery, 3.5 percent (1 of 29); distal left anterior descending artery, 3.5 percent (1 of 29); and distal circumflex artery, 7 percent (2 of 29). In 17 percent of cases (5 of 29) coronary spasm was noted at multiple sites. Seven patients (24 percent) were judged to have normal coronary angiograms when spasm was not evident; an additional four patients (14 percent) had only minimal atherosclerotic abnormality. The remaining 18 cases (62 percent) had spasm complicating significant fixed obstructive lesions (50 percent or more obstruction of luminal diameter); 34.5 percent (10 of 29) had additional evidence of significant fixed obstructive lesions in locations remote from areas of observed coronary spasm. Exclusive of left main stem spasm, the prevalence rate of single vessel spasm was 83 percent (20 of 24); double vessel spasm, 12.5 percent

TABLE II

Distribution of Coronary Spasm in 20 Men and 9 Women

Site	Men			Women			Total (29)		
	Underlying Lesion		no. of Cases	Underlying Lesion		no. of Cases	Underlying Lesion		no. of Cases
	>50%	⩽50%		>50%	⩽50%		>50%	⩽50%	
Left main stem	1	4	5	1	0	1	2	4	6
Right coronary artery									
Proximal	4	1	5	5	2	7	9	3	12
Distal	0	0	0	0	0	0	0	0	0
Left anterior descending coronary artery									
Proximal	3	8	11	0	2	2	3	10	13
Distal	0	0	0	1	0	1	1	0	1
Left circumflex coronary artery									
Proximal	0	0	0	1	0	1	1	0	1
Distal	1	0	1	1	0	1	2	0	2
Totals	9	13	22	9	4	13	18	17	35
Single vessel			15			5			20
Double vessel			1			2			3
Triple vessel			0			1			1

(3 of 24); and triple vessel spasm, 4 percent (1 of 24).

In 18 cases coronary injections were made during spontaneous chest pain. In each case coronary spasm produced maximal obstruction. Nitroglycerin or isosorbide dinitrate, administered sublingually, relieved chest pain in all but patient. Accordingly, in all but this case, relief of pain was accompanied by reduced or complete resolution of coronary obstruction.

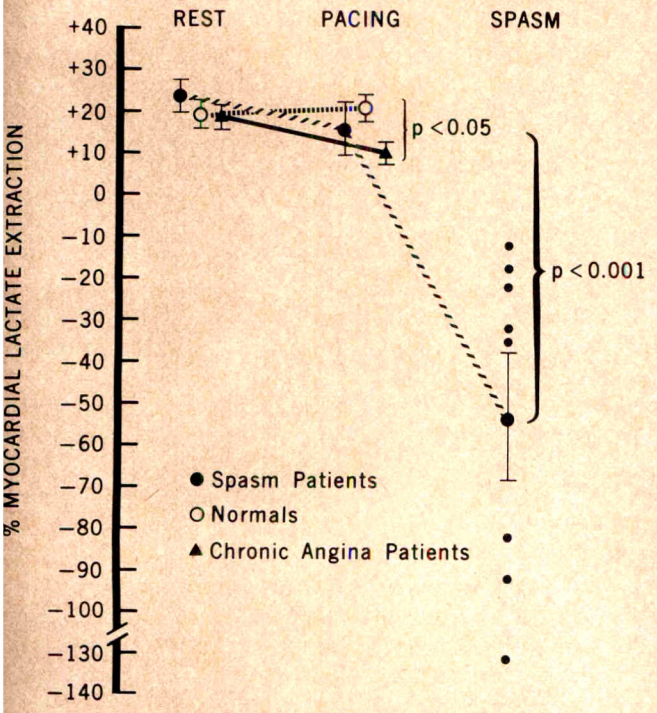


FIGURE 1. The mean myocardial lactate response to coronary sinus pacing (140 beats/min) among 15 patients with coronary artery spasm (+15.74 ± 6.66 percent) was not significantly different from that of normal subjects (+19.9 ± 3.0 percent). However, during acute coronary arterial spasm (spontaneous chest pain) marked myocardial lactate production is observed in each case. Patients with chronic stable angina (+10.30 ± 2.30 percent) usually experienced angina but showed only a small though significantly abnormal decrease in percent of myocardial lactate extraction after pacing.

TABLE III

Percent Myocardial Lactate Extraction in 15 Cases

Case no.	Rest Control	Pacing	Spontaneous Angina
1	39.4	27.8	−31.9
2	27.8	38.0	−17.9
6	13.2	32.0	. . .
7	34.2	34.7	. . .
8	20.7	22.7	. . .
9	13.6	19.6	. . .
10	0.0	0.0	−82.0
11	17.0	−42.0	−92.0
12	19.0	8.0	−12.0
17	34.7	. . .	−22.0
20	23.0	12.0	. . .
24	43.8	48.1	. . .
25	. . .	. . .	−132.7
26	32.7	−14.0	−35.0
27	16.7	17.7	. . .
Mean	23.99	15.74	−53.19
± SEM	±3.21	±6.66	±15.44

SEM = standard error of the mean.

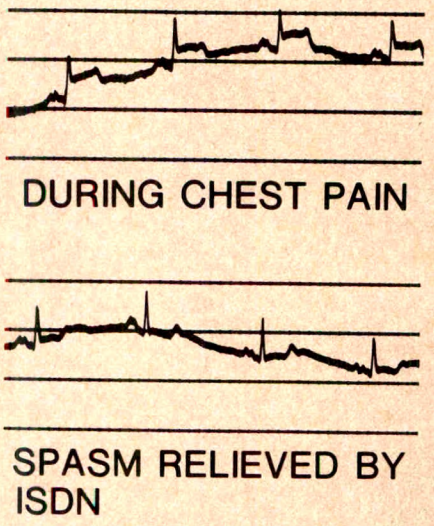


FIGURE 2. Case 20. During cardiac catheterization chest pain occurred spontaneously and was accompanied by S-T segment elevation (lead II). Prompt relief of pain and reduction of S-T elevation were afforded by sublingual administration of isosorbide dinitrate.

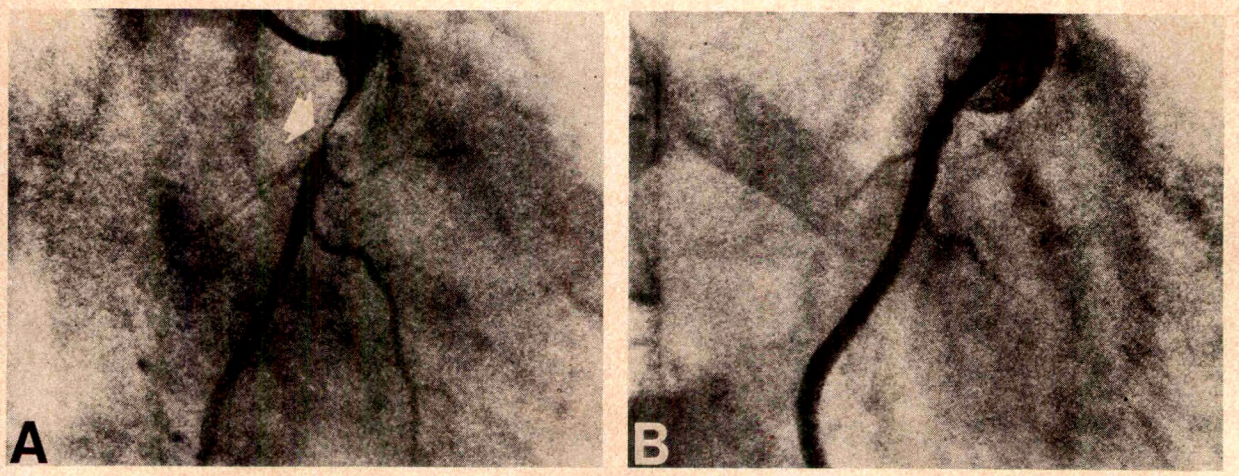


FIGURE 3. Case 20. Right coronary arteriogram, right anterior oblique view. **A,** after the onset of chest pain and before relief with isosorbide dinitrate. Marked spastic constriction **(arrow)** is evident at the proximal portion of the right coronary artery. **B,** after administration of isosorbide dinitrate, the spastic narrowing is observed to be completely relieved.

Evidence for collateral supply to the spastic ischemic region was infrequent. Retrograde visualization of the vessel distal to the constriction was seen in only 7 percent of patients (2 of 29) despite the critical extent of obstruction.

Left ventriculographic abnormalities included dyskinesia in two patients, both of whom had myocardial infarction in areas supplied by spastic vessels. Twelve patients had various degrees of hypokinesia related to spasm or combined spasm and fixed coronary obstruction. The majority (52 percent) had normal-appearing left ventriculograms.

Myocardial metabolic studies (Table III, Fig. 1): During spontaneous unprovoked angina, marked lactate production (−53.19 ± 15.44 percent) was invariable. However, coronary sinus pacing at 140 beats/min for 5 minutes failed to result in chest pain, S-T abnormalities or abnormal myocardial lactate extraction in 9 of 13 cases. Consequently, myocardial lactate extraction was significantly less abnormal than that observed during spontaneous chest pain (+15.74 ± 6.66 versus −53.19 percent ± 15.44) (P <0.001). Similarly, the effects of pacing were less significantly abnormal in this group of patients than in patients previously studied who had classic exertional angina pectoris (+15.74 percent ± 6.66 versus +10.30% ± 2.30) (P <0.05).

Clinical course and prognosis: Clinical observation following arteriographic recognition ranged from 2 to 24 months, averaging 12.6 months. All patients were initially treated with vasodilators, and most also received propranolol. Antiarrhythmic agents were required in 10 cases. In only three cases was medical therapy completely effective in alleviating recurrent anginal symptoms. Five patients were considered to be in improved condition despite occasional angina; 21 were judged intractable to medical management. Three patients continued to manifest ventricular tachycardia with antiarrhythmic therapy, and two experienced heart block with each seizure. Despite continued chest pain and arrhythmia, only one patient (1 of 11) died with medical management alone.

Coronary bypass surgery was considered the preferred treatment in 18 of 29 patients with intractable symptoms. After coronary surgery, the condition of nine patients (50 percent) was improved and that of five (28 percent) was unchanged; four patients (22 percent) died. The incidence of myocardial infarction during the period of study was 18 percent (2 of 11) in those treated solely by medical therapy and 22 percent (4 of 18) among patients after coronary bypass surgery.

The overall results of coronary bypass surgery performed concurrently by the same surgical team yielded a 76 percent incidence rate of symptom relief, an 11 percent incidence rate of perioperative myocardial infarction and a 2.7 percent operative mortality rate.

Case Illustrations

Case 20

Coronary spasm in normal coronary arteries causing transmural myocardial ischemia: A 49 year old white woman had her first attack of angina 1 year before admission for coronary angiography. Subsequently, she had anginal episodes several times a week. The chest pain would last minutes to hours and had no relation to activity or meals. The resting electrocardiogram was normal during pain-free intervals. Physical examination was within normal limits.

An initial arteriogram of the right coronary artery showed a normal angiographic outline. During spontaneous chest pain the electrocardiogram (lead II) showed S-T segment elevation (Fig. 2). Repeat right coronary visualization showed severe spastic stenosis of the proximal segment (Fig. 3A). After sublingual administration of isosorbide dinitrate (2.5 mg), the chest pain was relieved, the S-T elevation disappeared (Fig. 2) and the coronary arteriographic outline returned to normal (Fig. 3B).

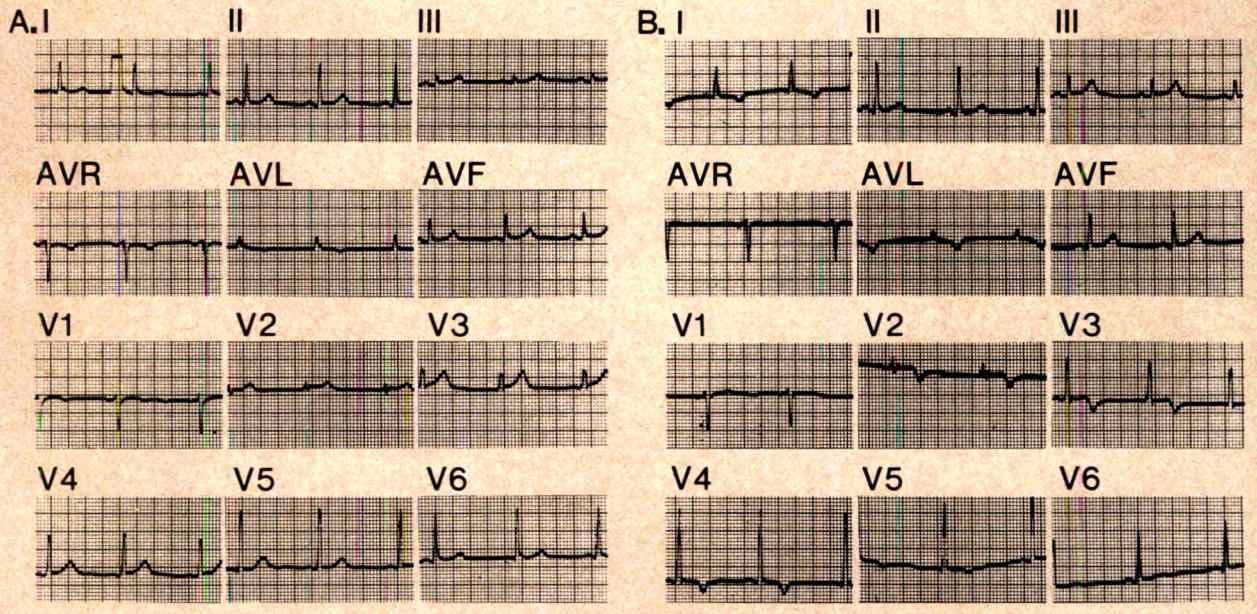


FIGURE 4. Case 16. **A,** control electrocardiogram in absence of angina. **B,** electrocardiogram during angina showing T wave inversion in leads I, aVL and V_2 to V_5, consistent with acute ischemia of the anterior left ventricular wall. After relief of pain the electrocardiogram returned to its control appearance.

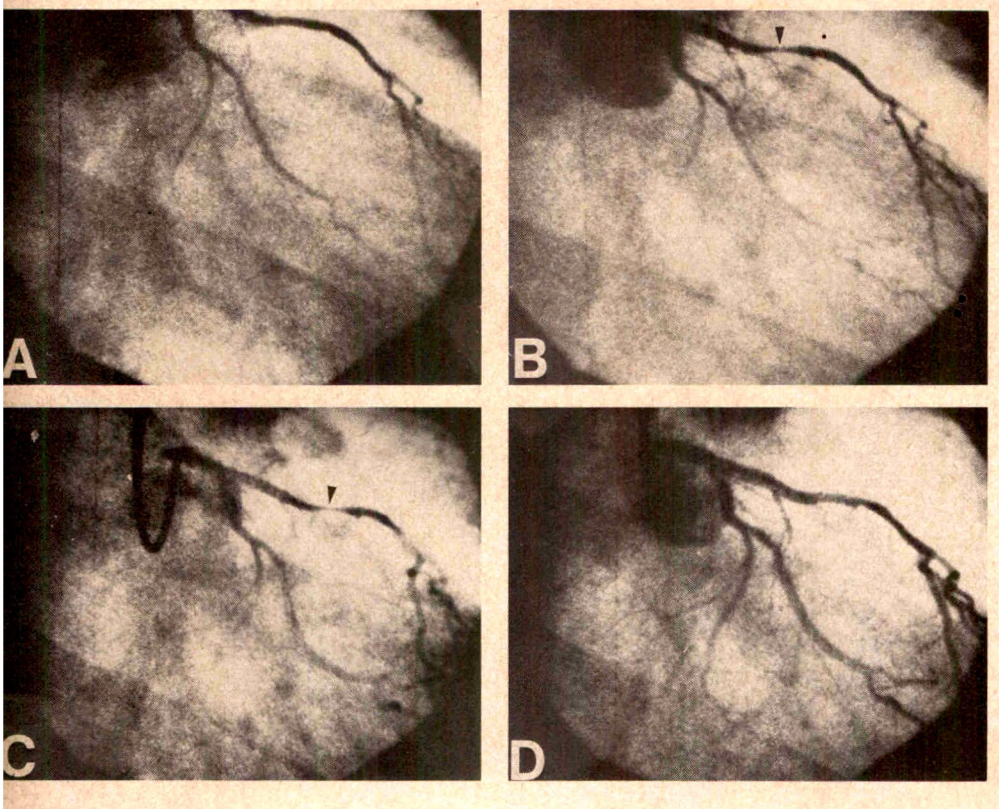


FIGURE 5. Case 16. Left coronary arteriogram, right anterior oblique projection. **A,** control study showing an essentially normal coronary outline. **B** and **C,** repeat left coronary injections during progressively increasing angina show increasing constriction **(arrow)** of the proximal left anterior descending artery (B → C). **D,** after administration of isosorbide dinitrate, the left coronary artery dilates and the focal constriction of the proximal left anterior descending artery disappears, leaving only minor luminal outline irregularity.

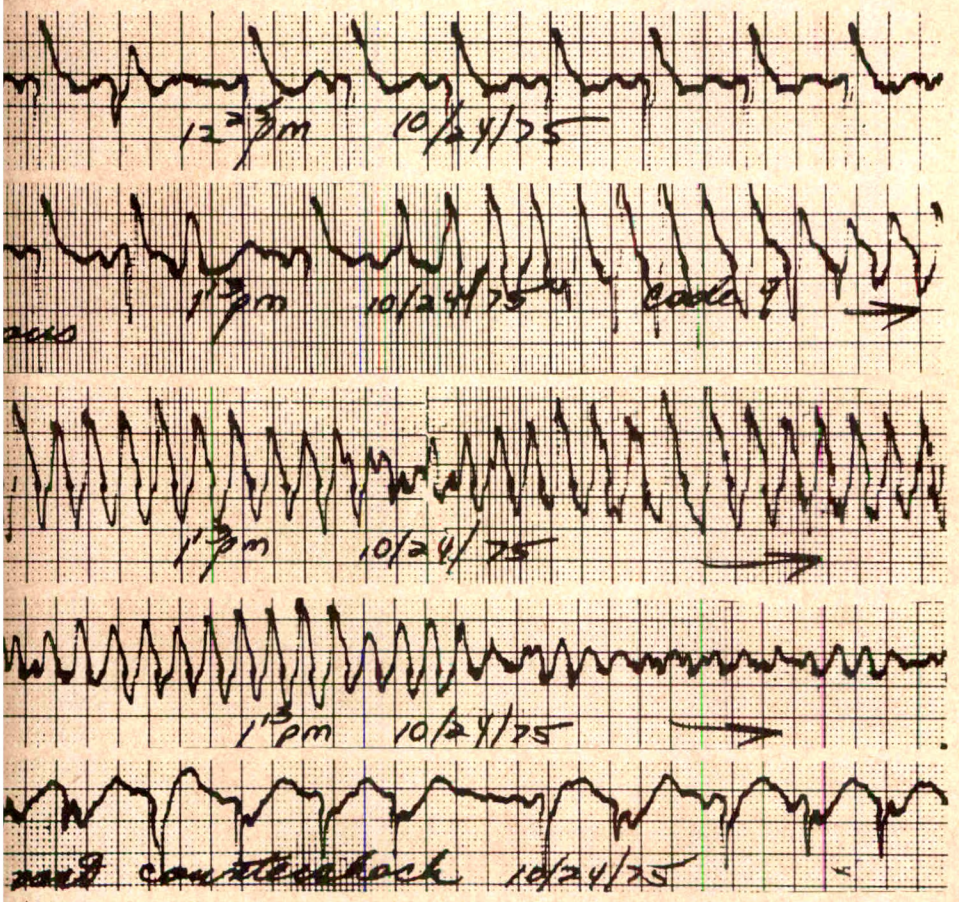


FIGURE 6. Case 12. An electrocardiogram monitoring strip during spontaneous chest pain. S-T segment elevation is followed by ventricular tachycardia and then ventricular fibrillation. After direct current countershock the rhythm is restored to normal **(bottom strip).**

Case 16

Coronary spasm causing subendocardial ischemia: A 48 year old white male executive had a history of recurrent nonexertional substernal pain for 2 years. The pain was usually relieved by sublingually administered nitroglycerin. An exercise electrocardiographic tolerance test was normal, despite a submaximal heart rate response. On physical examination the blood pressure was 140/90 mm Hg, and a grade 2/6 ejection systolic murmur was evident at the apex. The resting electrocardiogram was usually normal (Fig. 4A). However, during episodes of spontaneous chest pain, abnormal T wave inversion in leads I, aVL and V_2 to V_5 was invariably present (Fig. 4B).

Coronary arteriography showed the left anterior descending artery to have a normal outline initially (Fig. 5A). During angina, repeated injections demonstrated spastic constriction of the proximal left anterior descending artery (Fig. 5, B and C). After administration of isosorbide dinitrate, 5 mg sublingually, spastic obstruction was relieved and minor atherosclerotic irregularity was revealed (Fig. 5D).

Despite therapy with nitroglycerin, propranolol, isosorbide dinitrate and morphine, anginal episodes could not be satisfactorily controlled. The patient therefore underwent coronary bypass surgery but died in the immediate postoperative period as a result of intractable "pump failure." Postmortem examination demonstrated a patent aortocoronary bypass graft, a patent proximal left anterior descending artery displaying only mild atherosclerotic obstruction and acute subendocardial infarction of the anterior wall.

Case 12

Coronary spasm causing major ventricular arrhythmia: A 43 year old white woman had had substernal pain for 10 years. She was recently admitted to the cardiac care unit because of increasingly frequent and persistent chest pain. The pain was not necessarily related to exertion and was often accompanied by shortness of breath and nausea. Occasionally when the pain was sufficiently intense, syncope resulted. Physical examination was entirely within normal limits. During chest pain electrocardiograms were recorded showing S-T segment elevation in leads I, II, and V_2 to V_6. During a period of medically intractable angina, frequent premature ventricular contractions leading to ventricular tachycardia and ventricular fibrillation resulted (Fig. 6). On other occasions, angina elicited complete heart block.

Coronary arteriography revealed spasm in each of the three major coronary arteries during chest pain (Fig. 7). Repeat

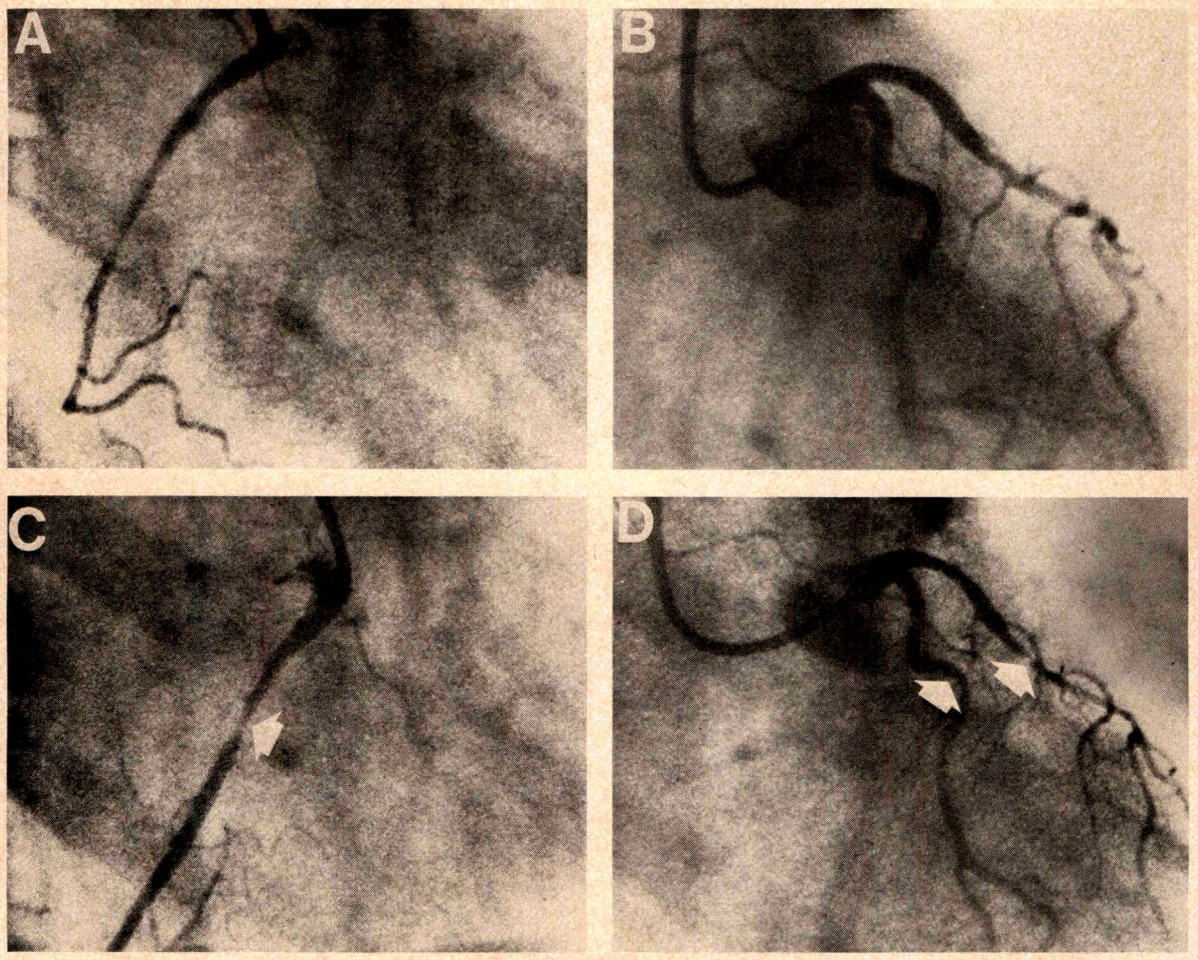


FIGURE 7. Case 12. Coronary arteriograms, right anterior oblique projection. During control injections, the right **(A)** and left **(B)** coronary arteries are essentially normal. During chest pain moderate spasm of the proximal right coronary artery is evident **(C, arrow).** The left coronary artery **(D)** shows marked constriction of the proximal left anterior descending artery **(right arrow)** and mild constriction of the proximal left circumflex artery **(central arrow).**

coronary arteriograms after sublingual administration of nitroglycerin (0.4 mg) showed normal coronary patency with minimal atherosclerotic irregularity.

Case 17

Coronary spasm causing myocardial infarction: A 67 year old white woman had a past history of inferior wall myocardial infarction complicated by second degree heart block and ventricular tachycardia 2 years before cardiac catheterization studies (Fig. 8A). Chest pain was usually nonexertional and ranged from a few minutes to hours in duration. Electrocardiograms recorded during pain showed S-T segment elevation in leads II, III and aVF (Fig. 8B). Relief with sublingually administered nitroglycerin or isosorbide dinitrate was usual but not invariable. Physical examination revealed that the patient was obese and had a grade 2/6 basal ejection systolic murmur.

Coronary arteriography demonstrated complete spastic occlusion of the proximal right coronary artery which resulted in ventricular fibrillation. Before spastic obstruction the right coronary artery was visualized without apparent obstruction. After restoration of normal sinus rhythm, a repeat right coronary arteriogram showed a normal right coronary outline (Fig. 9, A to C). Left ventriculography demonstrated inferior wall akinesia consistent with the history of prior inferior wall myocardial infarction (Fig. 9, D and E).

Despite a medical regimen that included isosorbide dinitrate, 10 mg sublingually every 3 hours; nitroglycerin 0.4 mg as needed, and propranolol, 40 mg 4 times a day, the patient continued to have chest pain as well as frequent premature ventricular contractions. Three months after coronary arteriography she died suddenly. Postmortem examination showed an atherosclerotic plaque at the origin of the right coronary artery. All three coronary arteries were free of obstruction. An old inferior wall myocardial infarction was accompanied by recent infarction in the adjacent tissue.

Discussion

The classic studies of Zoll et al.[10] have firmly established the correlation of typical angina pectoris with the pathologic anatomic findings of atheromatous narrowing in one or more major coronary arteries. Subsequently, Proudfit et al.[11] provided coronary angiographic support for this correlation. Hence, since coronary arterial spasm had been relegated to little more than a hypothesis, its role in the clinical manifestations of myocardial ischemia was viewed with skepticism. Recently, documentation[6,7,12–17] of coronary spasm as a cause of Prinzmetal's variant angina has resulted in a renewal of interest in the functional basis for myocardial ischemia. Our study suggests that coronary spasm has a wider spectrum of clinical presentation than previously acknowledged. Patients with coronary spasm manifest, in common, an atypical anginal syndrome complicated by arrhythmia, myocardial infarction and sudden death. In the majority of our patients, coronary spasm was accompanied by various degrees of atherosclerotic coronary artery disease. Accordingly, the symptoms, signs, electrocardiographic, hemodynamic and myocardial metabolic distinguishing features were somewhat impure. Nonetheless, an analysis of these characteristics was helpful in distinguishing these patients from those with typical exertional angina pectoris.

Differences from typical angina pectoris: Variant angina pectoris, as described by Prinzmetal et al.,[3] differs from typical angina pectoris in several features. Ischemia that is primarily dependent on coronary flow (coronary spasm) accounts for angina that occurs unpredictably with the subject at rest or during only mild activity. Depending upon the duration of spasm, angina may be fleeting or protracted. Ventricular arrhythmias and heart block often accompany angina resulting in lightheadedness and syncope as associated complaints. By contrast, fixed coronary atherosclerotic obstruction produces a more predictable anginal distress. The symptoms often correlate best with factors known to

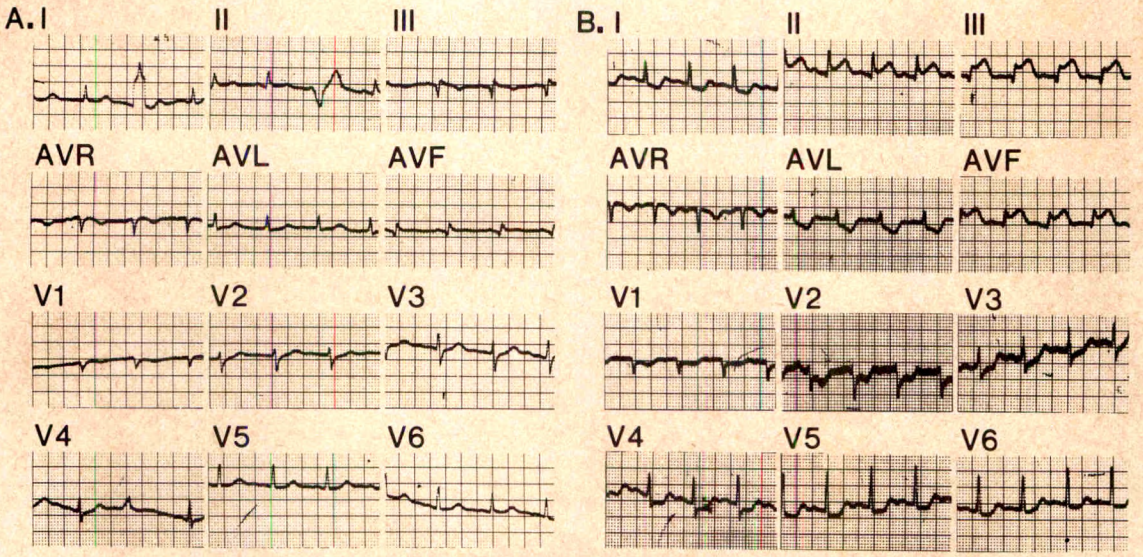


FIGURE 8. Case 17. Electrocardiograms. **A,** control tracing, showing evidence for old (2 years before admission) inferior myocardial infarction. Residual Q wave abnormalities are present in leads II, III and aVF. **B,** during spontaneous chest pain. S-T segment elevations are acutely evident in leads II, III and aVF with reciprocal S-T depression in leads I, aVL and V_1 to V_6. Relief of pain restored the electrocardiogram to the pattern observed in **A.**

increase myocardial oxygen demand. The pain subsides within 2 to 5 minutes in concert with an attenuation of the provocative factor (for example, physical effort). Typical angina pectoris is only occasionally associated with ventricular arrhythmia and therefore rarely results in lightheadedness or syncope.

Incidence of spasm: The incidence rate of coronary arterial spasm during coronary arteriography is reported to range from 0.26 to 0.93 percent.[17] Our 29 cases, detected over a 2 year period in 3,000 consecutive coronary angiographic studies reflect a 1 percent incidence rate. Coronary spasm is probably even more common than generally recognized. Recently, in a prospective search for this phenomenon, Chahine et al.[17] reported a significantly higher incidence rate: 2.93 percent. Several factors may contribute to the relatively low reported incidence rate: (1) failure to perform a systematic search for coronary spasm, (2) routine use of sedatives and tranquilizers as premedication for cardiac catheterization, (3) mild coronary vasodilator action of the angiographic contrast medium, (4) routine use of vasodilator drugs at the onset of coronary arteriography, (5) assessment of a coronary lesion as "fixed" if the obstruction persists despite subtle changes in its appearance after administration of nitroglycerin, (6) reluctance to visualize the coronary arteries during chest pain, and (7) avoidance of catheterization studies in patients during acute coronary syndromes when spontaneous spasm is most likely to be present.

Angiographic features of coronary spasm: The cardiac catheterizations were performed in all of our patients during the unpremedicated fasting state. By specific intent, coronary arterial opacification was performed in conjunction with the onset of chest pain and electrocardiographic change. Nitroglycerin or isosorbide dinitrate was not administered until after a full set of coronary arteriograms was completed. Angiographic studies were then repeated after nitrate administration. We, like others, have probably underestimated the incidence of coronary arterial spasm since our study was not prospective by design and our rigid criteria precluded any occurrence of spasm that could have been attributed to catheter irritation unless accompanied by electrocardiographic abnormalities. Despite these limitations, we have been able to ascribe certain angiographic features as suggestive of coronary spasm: (1) The lesion changes in configuration and extent; (2) despite coronary luminal obstruction estimated to be 90 percent or more, collateral supply to the ischemic region is rare; (3) single vessel obstruction is more common; and (4) sublingual nitrate administration usually relieves the spasm. In contrast, fixed coronary lesions producing angina pectoris usually involve two or more major coronary arteries,[18] and collateral vessels are commonly seen in regions where coronary obstruction exceeds 90 percent.[19–22] In the absence of spontaneous angina pectoris, the hemodynamic pattern was different from that observed in other studies of coronary

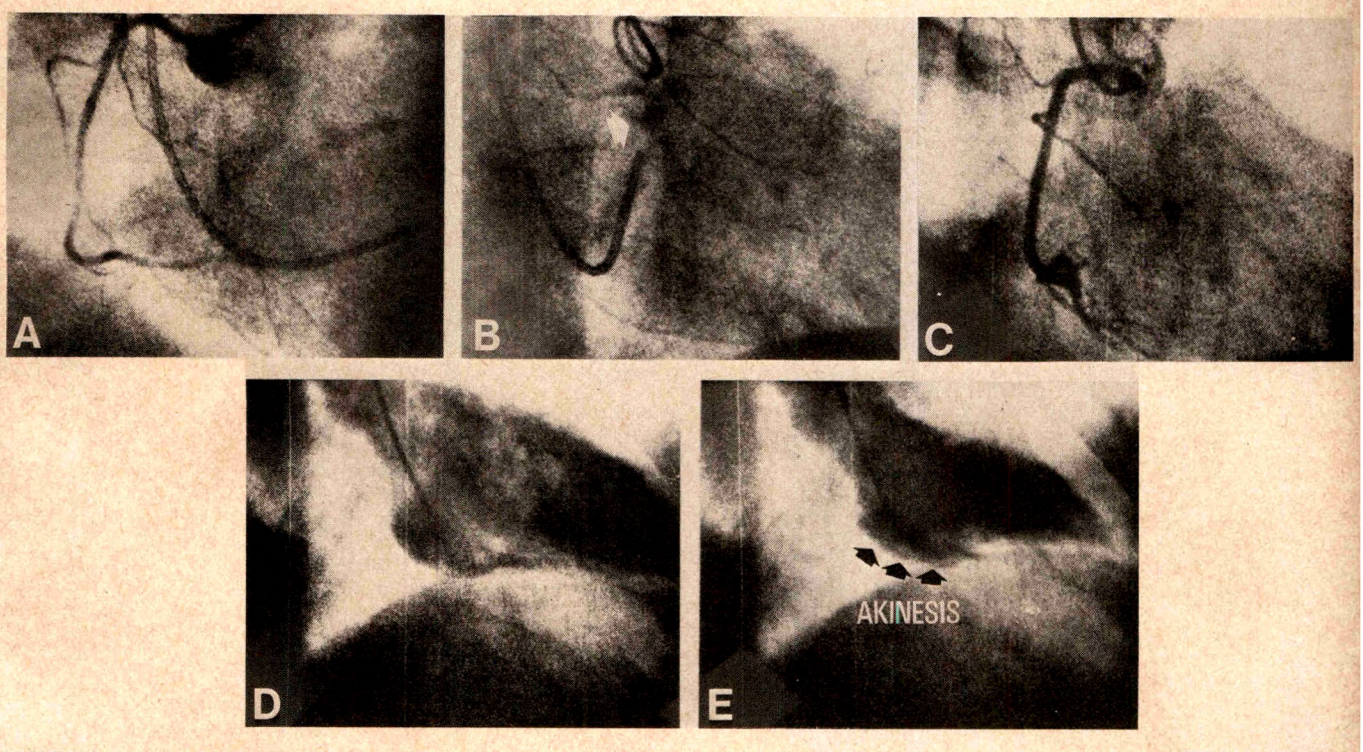


FIGURE 9. Case 17. Right coronary arteriograms in left **(A)** and right (**B** and **C**) oblique projections, and left ventriculogram, right anterior oblique projection (**D** and **E**). **A,** the right coronary artery has a normal outline. A catheter in the center of the field is situated in the coronary sinus. **B,** injection after the onset of chest pain reveals complete obstruction of the main trunk **(arrow)** of the right coronary artery. The coronary sinus catheter is now located toward the lower left of the field. **C,** a repeat right coronary arteriogram after recovery from ventricular fibrillation shows a normal right coronary outline. **D,** left ventriculographic frames during diastole **(D)** and systole **(E)** reveal akinesia of the inferior left ventricular wall **(arrows),** consistent with old inferior myocardial infarction.

heart disease.[23–25] In those few cases in which spastic anginal episodes were electrocardiographically and hemodynamically recorded, a frank hypodynamic state was manifested by reduced systolic blood pressure and little or no significant change in left ventricular end-diastolic pressure. Spontaneous anginal episodes recorded in patients presumed to have typical angina pectoris regularly are manifested by systemic hypertension and increased left ventricular end-diastolic pressure accompanying electrocardiographic abnormalities.[23–25]

Myocardial metabolic changes during coronary spasm: Our observations of the myocardial metabolic responses during spontaneous chest pain as well as during controlled tachycardia have not previously been reported. These findings, although not unexpected, appear to be unique to coronary spasm: That is, spontaneous angina invariably resulted in marked myocardial lactate production, whereas controlled tachycardia, in most cases, elicited no significant abnormality of myocardial lactate extraction or otherwise reflected abnormalities consistent with the degree of residual fixed coronary arterial obstruction.[26]

Medical versus surgical therapy: The clinical course of this selected group of patients poses a major therapeutic dilemma. Medical therapy including bed rest and administration of nitrates and propranolol was often only temporarily effective. In this context, Lange et al.[27] described major ischemic complications after withdrawal from long-term industrial exposure to nitroglycerin. They suggested that chronic nitroglycerin exposure resulting in vasodilatation may evoke homeostatic vasoconstriction leading to coronary arterial spasm. Propranolol therapy has been considered capable of inducing coronary artery spasm as well. Yasue et al.[28] described four patients whose variant angina increased after administration of propranolol. They considered coronary spasm in these cases to be mediated by unopposed alpha adrenergic receptors.

Two medically managed cases were marred by myocardial infarction, and in one case the patient subsequently died. Major ventricular arrhythmia including ventricular tachycardia and heart block persisted in seven patients despite antianginal and antiarrhythmic therapy. Because of the unstable progressive character of their angina, 18 patients with angiographically documented fixed obstruction underwent coronary arterial bypass grafting. Unfortunately, surgical therapy was even less rewarding. A large incidence of myocardial infarction, relatively high surgical mortality rate and persistence of angina postoperatively warrant extreme caution in the selection of these patients for surgery.[29–33] Consequently, the choice of appropriate therapy must be highly individualized according to both coronary arteriographic findings and the response to various drug regimens. Myocardial revascularization may be the only therapeutic alternative when medical therapy fails in the patient with spasm complicating a significant critically situated coronary atherosclerotic lesion. In contrast, in patients without significant fixed obstruction, the capricious nature of coronary spasm appears to offer no therapeutic rationale for coronary bypass surgery.

Conclusion

We, as well as others, have confirmed the clinical entity of coronary arterial spasm. Our data suggest that the true incidence of this disorder is greater than now recognized and remains to be determined. Spasm has been found in apparently normal coronary arteries and has also been observed in arteries with various degrees of atherosclerotic obstruction. The spectrum of clinical manifestations attributable to coronary spasm has been widened beyond that of Prinzmetal's variant angina. Myocardial ischemia induced by spasm may be manifested as subendocardial as well as subepicardial ischemia. The major clinical syndromes of coronary heart disease including angina pectoris, ventricular arrhythmia and myocardial infarction have each been observed to result from coronary arterial spasm.

Acknowledgment

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Afterload Reduction in the Management of Postinfarction Ventricular Septal Defect

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The primary goal in the medical management of ventricular septal defect complicating myocardial infarction is to support cardiac function and control symptoms, if possible, for a period of 4 to 6 weeks. If the patient survives this period, surgical correction of the defect is technically easier and safer. In many cases, however, cardiac function is severely compromised, intractable biventricular failure develops, early operation is necessary and the likelihood of successful repair is diminished.

We recently treated two such patients by means of afterload reduction with nitroprusside. In one patient, sublingually administered isosorbide dinitrate was later used, and prolonged survival was achieved after surgery. Hemodynamic investigations in both cases demonstrated that nitroprusside improved cardiac output without necessarily decreasing mean arterial pressure. The effect of nitroprusside on pulmonary blood flow and left to right shunt was variable: One patient demonstrated a decrease in the ratio of pulmonary to systemic blood flow, and the other did not. We conclude that afterload reduction with either intravenous or oral agents is a potentially useful measure in the management of patients with ventricular septal defect complicating myocardial infarction.

Ventricular septal defect complicates 1 to 2 percent of cases of acute myocardial infarction[1–3] and, in this setting, is associated with a very high mortality rate: 46 percent of patients die within the first week, approximately 90 percent within the first 2 months and 93 percent within the first year.[4] The defect must eventually be corrected surgically, but the operative mortality rate is very high when correction is performed within the first 6 weeks after infarction.[6] Recently, we treated two patients with ventricular septal defect after acute infarction by decreasing afterload with nitroprusside and isosorbide dinitrate, in attempts to prolong life so that subsequent surgical treatment could be more safely instituted.

Case Reports

Case 1

A 62 year old woman with an acute anterior wall infarction had neither a heart murmur nor congestive failure when first examined. Twenty-four hours later hypotension and gross pulmonary edema developed, and a new grade 4/6 pansystolic murmur was heard over the entire precordium. The patient was treated initially with dopamine and metaraminol. Cardiac catheterization performed that day showed evidence of severe biventricular failure, low cardiac output (as reflected by a widened arteriovenous oxygen difference of 9.8 vol percent), and a 3.3:1 left to right shunt at the ventricular level (Table I, Day 1). A left ventricular angiogram documented a ventricular septal defect in the mid to low muscular septum. The anterior half of the heart was markedly hypokinetic. Coronary angiography revealed a 90 percent stenosis in the proximal left anterior descending coronary artery, diffuse disease of the left circumflex artery, and 50 percent luminal narrowing of the distal right coronary artery.

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TABLE I

Case 1: Hemodynamic Data

		Day 2		Day 3		
	Day 1	Control	NTP	Control	NTP 1	NTP 2
Nitroprusside (ng/min)	0	0	25	0	35	70
Mean pressures (mm Hg)						
Pulmonary artery	28	30	28	27	23	24
Systemic artery	74	85	75	84	82	70
Hemoglobin (g/100 ml)	13.1	11.8	11.0	11.2	11.2	10.5
O_2 content (vol %)						
Mixed venous (MV)*	7.1	7.2	9.6	6.6	7.8	6.7
Pulmonary artery (PA)	13.4	13.1	11.9	13.0	12.7	11.2
Systemic artery (SA)	16.9	15.4	15.5	15.1	15.1	13.4
$\dot{V}O_2$ (ml/min)†		208	216	172	246	219
Blood flow (liters/min)						
Systemic		2.5	3.7	2.0	3.4	3.3
Pulmonary		9.0	6.0	7.5	9.5	9.1
L to R shunt		6.5	2.3	5.5	6.1	5.9
CI (liters/min per m^2)		1.4	2.0	1.1	1.8	1.8
QP:QS	3.3:1	3.6:1	1.6:1	3.7:1	2.8:1	2.8:1
a-v O_2 diff (vol %)	9.8	8.2	5.9	8.5	7.3	6.7

*Mixed venous oxygen content, calculated using the formula[11,12]: $MV = \frac{(3 \times SVC) + IVC}{4}$

†Systemic blood flow (SBF) = $\frac{\dot{V}O_2/10}{\Delta O_2 \text{ content (SA–MV)}}$; pulmonary blood flow (PBF) = $\frac{\dot{V}O_2/10}{\Delta O_2 \text{ content (PV-PA)}}$. Systemic arterial saturation was 95 percent or more in all cases. Therefore, pulmonary venous oxygen content was assumed to be equal to systemic arterial content.

a-v O_2 diff = arteriovenous (systemic artery — mixed venous) difference in oxygen content; CI = cardiac index = systemic blood flow/body surface area; L to R shunt = left to right shunt = pulmonary blood flow — systemic blood flow; NTP = nitroprusside infusion; QP:QS = ratio of pulmonary to systemic blood flow; $\dot{V}O_2$ = per minute oxygen consumption determined by analysis of timed collection of expired air.

Nitroprusside therapy: Infusion of nitroprusside was begun. A peripheral arterial catheter and a flow-directed pulmonary arterial catheter were introduced. After informed consent was obtained from the patient and family, a double lumen, flow-directed catheter was positioned with one orifice in the superior and the other in the inferior vena cava. Oxygen consumption was measured with analysis of timed collections of expired air. Cardiac output and shunt flow were measured serially at various rates of nitroprusside infusion (see Table I for the formulas used).

Nitroprusside was infused initially at a rate of 25 μg/min. The mean arterial pressure was decreased from 85 to 75 mm Hg, with an immediate increase in the systemic blood flow, a decrease in the pulmonary blood flow and left to right shunt (Table I, Day 2). The pulmonary to systemic flow ratio (QP:QS) decreased from 3.6:1 to 1.6:1. There was a dramatic improvement in clinical status: Diaphoresis diminished, the limbs warmed, and the sensorium cleared. The following day, nitroprusside was temporarily discontinued and then infused at two different rates (35 μg/min and later 70 μg/min). At the lower infusion rate, the mean arterial pressure was essentially unchanged; at the higher rate, it was decreased by 12 to 15 mm Hg (Table I, Day 3). At both dosages, nitroprusside increased systemic blood flow and decreased the pulmonary to systemic flow ratio. However, unlike the findings on Day 2, the pulmonary blood flow also increased, and the left to right shunt was not appreciably changed. Thus, nitroprusside produced similar hemodynamic effects at both dose levels, even though with the smaller dose the mean arterial pressure was essentially unchanged from control level.

Surgery: Despite the continued administration of nitroprusside at rates of 30 to 50 μg/min, as well as other supportive measures, including administration of digitalis and diuretic drugs, the patient's clinical status deteriorated. By the fifth hospital day, she had severe cardiogenic shock and was operated upon. At operation, the distal and midportions of the septum were infarcted. The septal defect measured 2 by 1 cm. The left ventricular wall was necrotic along its distal third, as was the area of the right ventricle adjacent to the septum. The defect was repaired, but the patient was unable to maintain adequate perfusion postoperatively, and she died.

Case 2

A 46 year old man who had a history of previous inferior myocardial infarction was hospitalized with an acute anterior infarction. Eighteen hours after admission he became diaphoretic and had a new grade 3/6 systolic murmur and bibasilar rales. At the bedside, a triple lumen flow-directed catheter was introduced into the pulmonary artery. Oxygen samples revealed a stepup in oxygen saturation in the right ventricle, thus supporting the clinical impression of interventricular septal defect with a left to right shunt. A catheter was also placed in the right radial artery.

Nitroprusside and isosorbide dinitrate therapy: A nitroprusside infusion was begun, and the infusion rate was increased until the pulmonary arterial wedge pressure decreased from 24 to 15 mm Hg. This was accomplished at an infusion rate of 65 μg/min, without a significant change in the peripheral arterial pressure (115/85 mm Hg before and 115/60 mm Hg after infusion of nitroprusside). For the first 3 hospital days the mean pulmonary arterial wedge pressure was held between 15 and 20 mm Hg. When the patient's clinical status stabilized, transition to oral peripheral vasodilator therapy was begun, using sublingually administered isosorbide dinitrate at a dose of 5 mg every 3 hours. The nitroprusside infusions were gradually decreased and eventually discontinued. Pulmonary diastolic pressure remained at 18 mm Hg and peripheral arterial pressure was 105/65 mm Hg while the patient was receiving isosorbide dinitrate sublingually, 10 mg every 3 hours. The pulmonary arterial catheter was removed.

During this time, the patient also received digitalis and diuretic drugs, and quinidine for control of ventricular irritability.

About 3 weeks after the infarction, progressive hepatic enlargement and tenderness developed, as well as nausea and vomiting. Diagnostic cardiac catheterization and coronary angiography, performed 1 week later, demonstrated severe three vessel coronary artery disease, inferior wall hypokinesia, a large anteroseptal and apical aneurysm and a ventricular septal defect. Hemodynamic measurements were made during the control state (with the patient receiving isosorbide dinitrate, 5 mg every 90 minutes) and during an infusion of nitroprusside at a dose of 90 μg/min. Nitroprusside produced an increase in systemic blood flow (from 3.4 to 4.6 liters/min), pulmonary blood flow (from 9.8 to 13.0 liters/min) and left to right shunt (from 6.4 to 8.4 liters/min) without significantly reducing mean arterial pressure (from 78 to 76 mm Hg). There was no significant change in pulmonary to systemic flow ratio.

Surgery: The patient subsequently underwent infarctectomy and surgical repair of the ventricular septal defect 4 weeks after admission. He had a relatively uncomplicated postoperative period and has had a satisfactory postoperative result.

Discussion

Nitroprusside has previously been used in patients with myocardial infarction without intracardiac shunts.[8,9] In the presence of congestive failure or clinical shock, nitroprusside increases stroke volume and cardiac index and decreases left ventricular filling pressure. The improvement is accompanied by a slight decrease in coronary blood flow, myocardial oxygen consumption and transmyocardial oxygen extraction.[9] In acute mitral regurgitation complicating myocardial infarction, nitroprusside increases forward cardiac output and forward stroke volume, and reduces systemic vascular resistance and regurgitant flow.[10]

In Case 1, nitroprusside initially reduced left to right shunting and improved forward cardiac output. The patient's clinical status was temporarily improved, but this beneficial response could not be maintained and early operation was necessary. Operation cannot be delayed when the clinical state of such patients deteriorates despite intensive medical therapy.[3,6]

In Case 2 the patient responded well to afterload reduction using nitroprusside followed by sublingually administered isosorbide dinitrate. He survived for 4 weeks after the septal rupture, with a 3:1 left to right shunt. Nevertheless, surgery was eventually required because of progressive right heart failure.

Our findings indicate that afterload reduction with either intravenous or oral agents is a potentially useful adjunct in the medical management of ventricular septal defect complicating acute myocardial infarction. The goal of medical management in this setting is to stabilize or improve the patient's cardiac function for 4 to 8 weeks. If this goal can be achieved, the margins of the infarct and of the ventricular septal defect will contain sufficient fibrous tissue to make surgical repair easier and safer.

The principal beneficial effect of nitroprusside is improvement in systemic blood flow (cardiac index); this can often be accomplished without significant change of the systemic arterial pressure, as demonstrated in both of our cases. The left to right shunt and pulmonary to systemic flow ratio may or may not decrease, depending upon the relative changes in systemic and pulmonary vascular resistance. In contrast, inotropic agents often increase afterload and shunt flow as well as left ventricular work and myocardial oxygen demands. These are relatively adverse hemodynamic consequences, and for this reason, such inotropic agents should be avoided if possible. In our two cases, the use of nitroprusside with careful hemodynamic monitoring was sufficiently promising to suggest the need for further trial of this approach in patients with ventricular septal defect complicating myocardial infarction.

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Pulmonary Arterial Compression Syndrome Caused by False Aneurysm of Left Ventricular Outflow Tract

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A 29 year old man experienced exertional dyspnea and coughing 3 1/2 years after insertion of a Braunwald-Cutter aortic valve prosthesis. Clinical examination suggested pulmonary arterial hypertension, and cardiac catheterization revealed a saccular lesion apparently arising from the left ventricular outflow tract and producing compression of the right pulmonary artery. Origin from the left ventricular outflow tract just under the aortic ring was confirmed at operation. The lesion apparently arose from an anular excavation related to previous endocarditis with abscess formation. Reported cases of similar aneurysmal lesions are briefly reviewed, and other known causes of the pulmonary arterial compression syndrome are discussed.

External compression of the pulmonary artery is an uncommon problem and has rarely been recognized clinically. Aneurysms of the left ventricular outflow tract are equally rare and have not been reported to cause compression of extracardiac structures. We report herein an unusual false aneurysm of the heart causing extrinsic pulmonary arterial compression.

Case Report

The patient, a 29 year old man, was discovered to have a murmur of aortic insufficiency during a preemployment physical examination in December 1969. He had no history of previous cardiac disease or rheumatic fever. In 1972 he was admitted to the University of Alabama Medical Center with significant exercise intolerance and signs of severe aortic insufficiency. He underwent aortic valve replacement in September 1972. At operation, the aortic valve leaflets were abnormally thickened, probably as a result of rheumatic fever. A surprising finding was a 4 mm perforation at the base of the left coronary cusp and a smooth-walled excavation of the aortic anulus in the region of the perforation. These changes were believed to represent healed endocarditis, and the excavation was interpreted as the residuum of a previous abscess at that site. The aortic valve was excised, and a Braunwald-Cutter aortic prosthesis was inserted. After operation, the patient initially did well, but in August 1974 he sustained an acute inferior myocardial infarction that was thought to be embolic in origin. His recovery was uneventful and he remained well until September 1975, when exercise intolerance, characterized by exertional dyspnea and coughing, developed and progressed over the next 3 months until his physical activity was severely limited. He had one near syncopal episode after walking.

On readmission in December 1975, his blood pressure was 100/70 mm Hg. Carotid pulsations were diminished without delayed upstroke. The chest was clear. Cardiac examination revealed a prominent apical impulse with lateral displacement and a left parasternal lift; the first heart sound was normal, and the pulmonary component of the second sound was increased and palpable. Normal prosthetic sounds were present. A grade 3/6 systolic ejection murmur was heard at the left sternal border with radiation to the base and apex. A grade 2/6 early diastolic murmur was heard at the upper left sternal border. An electrocardiogram revealed an old inferior myocardial infarction, right axis deviation and S-T segment elevation in the inferior and lateral leads. A chest roentgenogram disclosed an enlarged heart with an unusual convexity of the upper left

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heart border (Fig. 1). Results of complete blood count and chemistry profile and erythrocyte sedimentation rate were normal; blood cultures were sterile.

At cardiac catheterization, right ventricular pressure was 66/7 mm Hg, main pulmonary arterial and left pulmonary arterial pressures 66/14 mm Hg and left pulmonary wedge pressure 11 mm Hg. Right pulmonary arterial pressure was 22/10 mm Hg, and on pullback a systolic pressure gradient of 44 mm Hg was noted at the junction of the main pulmonary artery (Fig. 2). Cardiac index was 3.22 liters/min per m^2. Contrast material injected into the main pulmonary arterial trunk demonstrated a long smooth-walled indentation of the right pulmonary artery in diastole with marked narrowing in systole (Fig. 3). Follow-through films showed normal pulmonary veins and downward compression of the left atrium. The left ventricle was normal in size and contour. As dye passed through the left ventricle and into the aorta, a large chamber lying between the left atrium and pulmonary artery was opacified (Fig. 4). Biplane retrograde aortogram showed a normal-appearing aortic root and prosthetic valve, no aortic regurgitation and no opacification of the saccular lesion. Coronary arteriographic findings were normal. Diagnosis after catheterization was false aneurysm of the left ventricular outflow tract causing pulmonary arterial compression and significant pulmonary hypertension.

At operation on December 19, 1975, a large false aneurysm was found behind the aortic root. The attachments of the Braunwald-Cutter prosthesis were intact and, after removal of the prosthesis, an opening 1.2 cm in diameter was seen arising in the subvalvular area in communication with the posterior false aneurysm. The ostium of the aneurysm was closed by oversewing during insertion of a Bjork-Shiley aortic valve prosthesis. The postoperative course was uneventful, and the patient was discharged on December 26, 1975. At follow-up examination 5 months later, he was doing well.

Discussion

The patient's aneurysmal lesion was almost certainly the result of the previous infective endocarditis revealed at the initial operation in September 1972. The ostium of the aneurysmal lesion arose from the anular excavation previously noted. This excavation probably represented the site of previous abscess formation, which underwent eventual dilatation and aneurysm formation because of structural weakness in the wall and the hemodynamic stresses of ventricular contraction.

Ventricular outflow aneurysms: Aneurysmal lesions of the left ventricular outflow tract are quite rare. They have been described as examples of separation of

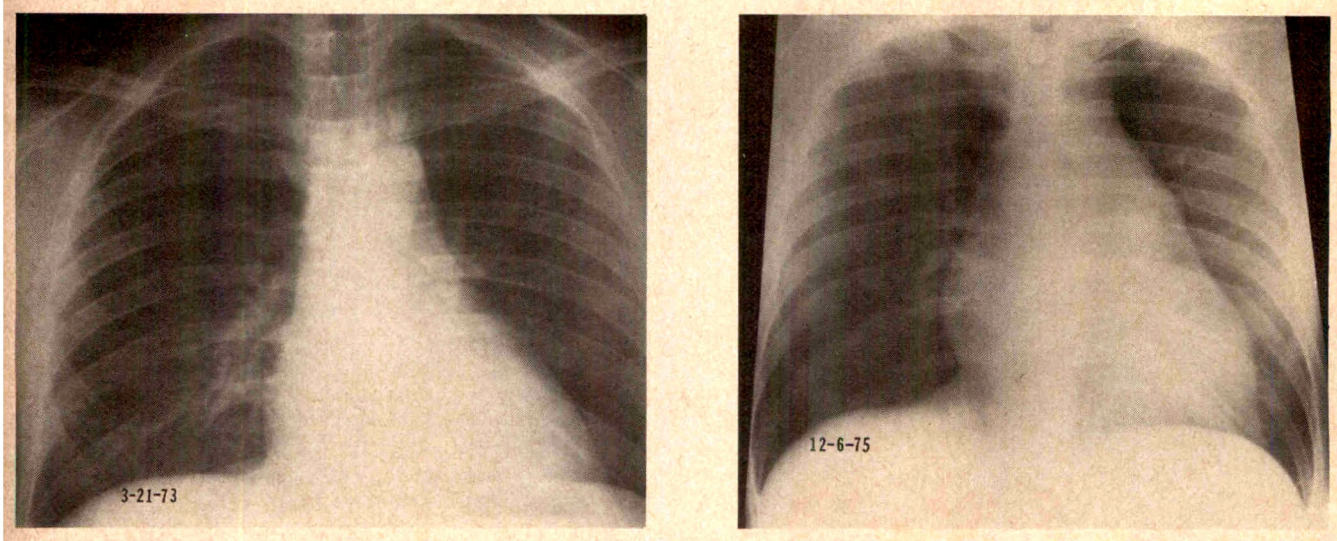


FIGURE 1. Chest roentgenograms. **Left,** film of March 1973 showing only residual cardiomegaly after aortic valve replacement in September 1972; **right,** film of December 1975 showing convexity at upper left cardiac border.

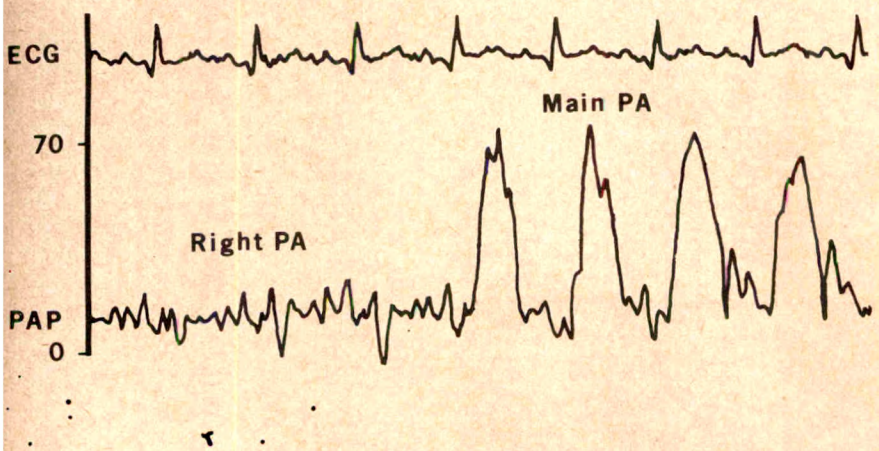


FIGURE 2. Pullback pulmonary arterial pressure (PAP) tracing from the right to the main pulmonary artery (PA) demonstrating peak systolic gradient of 44 mm Hg. ECG = electrocardiogram.

the aorta from the heart,[1] anular subvalvular aneurysms,[2–4] fibrous body aneurysms[5] and aneurysms of mitral-aortic intervalvular fibrosa.[6] Lesions described as separation of the aorta from the heart may arise above the valve leaflets in the sinuses of Valsalva, below the leaflets within the anulus or at both sites. They may be seen alone or in association with inflammatory processes, particularly infective endocarditis. Lesions occurring above the leaflets are aneurysms of the sinus of Valsalva, and are well recognized as a distinct clinical entity. Those arising below the valve leaflets within the anulus are much less common and are properly called ventricular aneurysms.

Anular subvalvular aneurysms have been described in the South African Bantu and in Nigerians.[2–4] They arise in relation to the aortic and mitral valve rings at

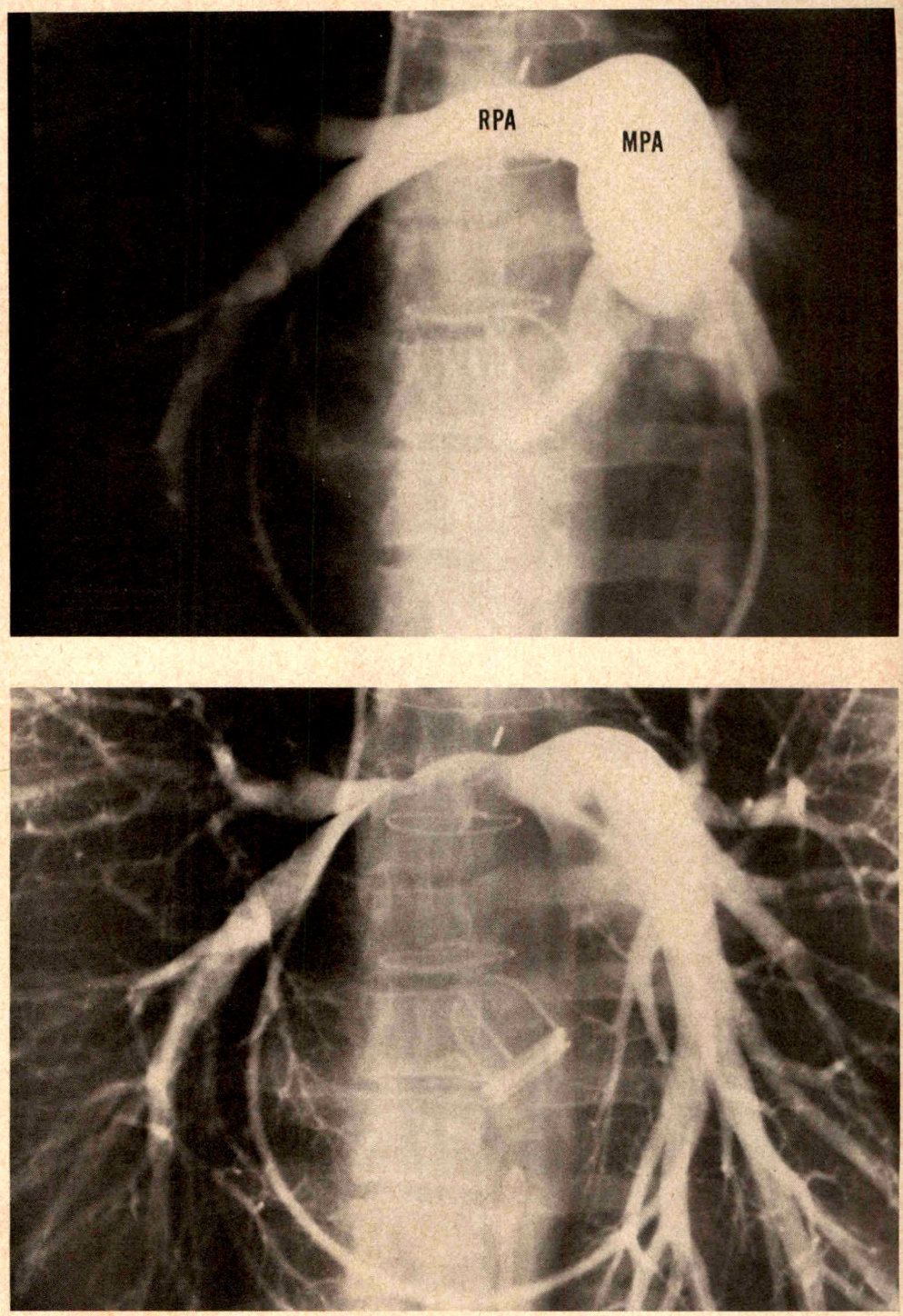


FIGURE 3. Pulmonary arteriogram after injection of contrast medium into the main pulmonary artery (MPA). **Top,** diastolic frame showing slight indentation of the right pulmonary artery (RPA) by external mass. **Bottom,** systolic frame showing marked compression of the right pulmonary artery by the external mass.

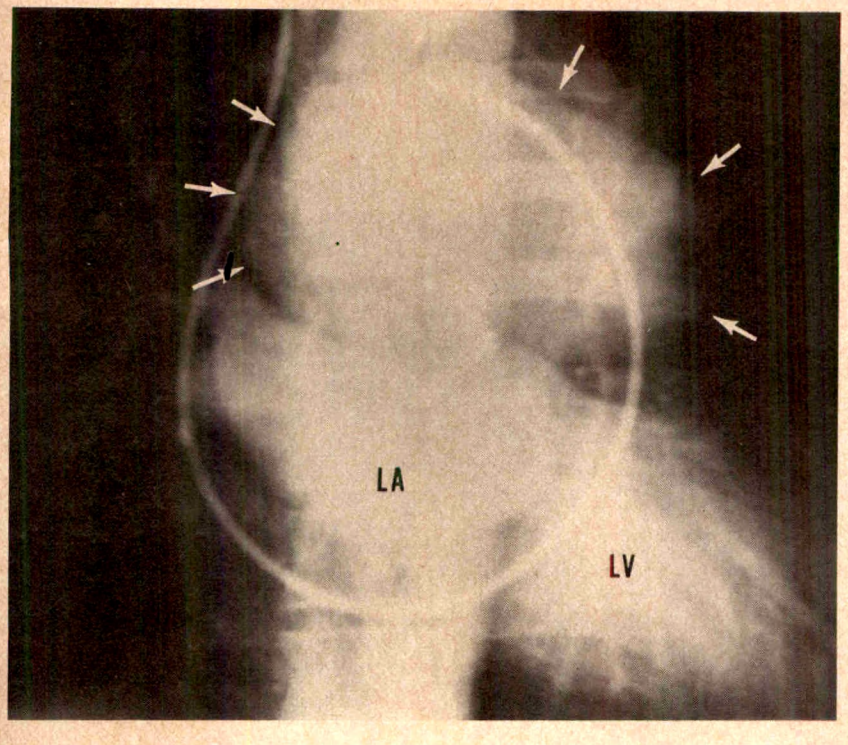


FIGURE 4. Late levophase of pulmonary arteriogram showing opacification of a large mass (**outlined by arrows**) superior to the left atrium (LA) and left ventricle (LV) and presumably posterior to the aorta.

the base of the heart and are thus distinct from the more common left ventricular aneurysms seen in ischemic heart disease. Their true etiology is unknown, although congenital factors are considered important by some.[2,3] Mitral anular lesions are usually large and often have multiple ostia.[2] The subaortic anular lesions are usually small and are likely to be incidental findings at autopsy although they may cause significant aortic insufficiency by dissecting around the anulus and undermining the supporting valve tissue.[2,4]

Isolated case reports in Europe and the United States have described similar lesions involving the subvalvular area designated anular subvalvular aneurysms[7–9] or fibrous body aneurysms.[5] They have occurred in patients with associated conditions to which the lesions could be attributed. The most common associated condition has been infective endocarditis, although trauma[9] and rheumatic valve disease without endocarditis[7] have also been noted.

Lesions in the mitral-aortic intervalvular fibrosa have also been reported.[6] Although they do not arise strictly in the tough fibrous tissue of the anulus, they do arise within the ventricle in close anatomic proximity to the anulus. Known reported cases have all been associated with infective endocarditis.

These aneurysmal lesions of the left ventricular outflow tract are quite uncommon, and compression of extracardiac structures has not been reported in association with them. Extrinsic compression of the pulmonary artery, as seen in our patient, is equally uncommon and may be caused by several other processes.

Pulmonary arterial compression: External compression of the pulmonary artery or its main branches is well recognized as a consequence of syphilitic aneurysm of the ascending aorta.[10–14] Often there is associated rupture of the aneurysm into the pulmonary artery, creating an aortopulmonary fistula, which may dominate the clinical findings.[15] A few reports of compression of the pulmonary artery due to aneurysms of the descending aorta have appeared. These have been due to trauma[16] or atherosclerosis[17] and have more frequently involved the left pulmonary artery than the main pulmonary arterial trunk. Acute dissection of the ascending aorta may also cause pulmonary arterial compression[18,19] and may simulate acute massive pulmonary embolism when it involves the main pulmonary arterial trunk.[19]

External compression of the pulmonary artery due to nonvascular causes is usually due to an intrathoracic neoplastic or inflammatory process. Tumors causing pulmonary arterial compression have included teratomas,[14,20] Hodgkin's disease[20,21] and others.[14,22,23]

Inflammatory processes including adhesive rheumatic pericarditis[24] and chronic fibrous mediastinitis[25] have occasionally caused significant pulmonary arterial compression. Other reported causes include lymphatic cysts,[26] hilar lymph node enlargement[27] and, perhaps most unusual, callus formation of the sternum.[28]

Clinical correlations: An interesting feature of our case was the finding of pulmonary arterial hypertension in the face of unilateral pulmonary arterial obstruction. Our patient had significant obstruction of only his right main pulmonary artery with a peak systolic pressure gradient of 44 mm Hg (Fig. 2). There was no demonstrable main pulmonary arterial involvement by pullback pressure measurements or by pulmonary angiography. Yet clinical findings of pulmonary arterial hy-

pertension were present, as manifested by evidence of right ventricular lift, accentuated pulmonary component of the second sound and right axis deviation in the electrocardiogram. Experimental and clinical studies have shown that occlusion of the right or left pulmonary artery[29] or absence of one lung[30] is not sufficient to cause pulmonary arterial hypertension in the normal person. This may not be the case in the presence of other systemic disease, as evidenced by reports of cor pulmonale in patients with isolated obstruction of the right or left pulmonary artery.[11,14]

Another unique feature in our case was the dynamic nature of the pulmonary arterial obstructive process. Significant compression of the right pulmonary artery was present only during systole (Fig. 3). This systolic accentuation of obstruction is probably due to systolic expansion of the aneurysmal sac during ventricular ejection. Our observations were made only at rest, and it is quite likely that the physiologic consequences of the dynamic narrowing were intensified with exertion because of a combination of hemodynamic factors, including increased heart rate and its associated shortening of diastole. Exertionally related increases in myocardial contractility and left ventricular pressure may have further increased the size of the aneurysmal lesion, allowing further compression of the right pulmonary artery during both systole and diastole, and perhaps causing involvement of the main pulmonary arterial trunk, which was not seen at rest. Additionally, further aneurysmal expansion could increase left atrial compression and impede pulmonary venous return, aggravating the pulmonary hypertension. The interplay of these various factors could explain the magnitude of our patient's exertional symptoms in the face of relatively moderate hemodynamic abnormalities found at catheterization during rest.

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LYMPHATICS AND MYOCARDIAL FUNCTION

The patient with extensive subendocardial fibroelastosis described by Libanoff and McMahon[1] merits some discussion. I believe that he manifested certain findings compatible with disease involving the lymphatics of the heart.

The lymphatics of the mammalian heart drain from the endocardium to the epicardium, and on the ventricular surface the collecting lymphatics follow the veins.[2] There is evidence that diffuse disease of the myocardium, as well as disease of the myocardial lymphatics, can interfere with lymph drainage from heart muscle and lead to endocardial fibroelastosis in man.[3] Studies in dogs have shown that interference with lymph flow from the heart results in endocardial fibroelastosis.[4] It is known that interference with lymph flow predisposes to the laying down of fibrous tissue in the affected tissue[5–7] and that fibrotic processes related to wound healing are also altered.[8]

The phrase "delayed immunologic reaction" used by Libanoff and McMahon is a type of hazy terminology that does not tell us about the *mechanism* by which an inflammatory reaction might lead to severe endocardial fibroelastosis. In the patient presented such a reaction could have injured lymphatics and might then have interfered with lymphatic drainage by direct lymphatic obstruction. Additionally, because of an epicarditis, there could have been interference with the lymphatic drainage vessels on the surface of the heart. The mechanism of formation of pericardial effusions has also been related to impaired lymph and venous blood flow from the myocardium,[9] and the epicarditis in the patient described would be consistent with this concept.

Thus, a "delayed immunologic reaction" might cause endocardial fibroelastosis through diffuse direct injury to lymphatics and an inflammatory epicardial process, both causing interference with lymph flow. Certain viral infections may act in a similar manner.

The lymphatics of the heart are technically difficult to study, and much of the thinking surrounding their function in pathophysiology is indeed speculative. But enough work has been done to merit for them a role in our thinking. It is my opinion that they play an integral part in myocardial function in health and disease.[10]

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REPLY

We stated early in our article: "Eosinophilia occurs as a manifestation of many different disease processes; however, the mechanism by which it is induced has remained enigmatic." Our intention in the Discussion was to relate the endomyocardial fibrosis (a late phenomenon) to the eosinophilia (an early phenomenon). Other early manifestations of endomyocardial disease were of a diffuse nature involving the liver, spleen, lymph nodes and bone marrow. It should be noted that the lymph nodes were involved; perhaps the lymphatics were related to that involvement. This would be consistent with Miller's view that lymphatic obstruction of the heart caused the endomyocardial fibrosis. It is interesting that interference with lymph flow in the heart of the dog causes endomyocardial fibrosis.

Let us assume that a diffuse inflammatory reaction of the myocardium caused obstruction to the lymphatic flow. This could have been responsible for the endomyocardial fibrosis. Questions persist concerning etiology. What caused the diffuse myocardial inflammation? What role can one attribute to the eosinophil in the origin of this inflammation? Does the eosinophilia occur in response to the inflammation or as an initial response to some other stimulus?

I agree that the lymphatics merit a role in our thinking about pathologic findings of the heart, and I feel somewhat remiss in not considering their possible role in endomyocardial fibrosis.

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PRINZMETAL'S VARIANT ANGINA

Higgins et al.[1] leave the reader with the impression that two separate pathogenetic mechanisms caused variant angina in their 17 patients. They describe a group of eight subjects without important fixed coronary obstructive disease whose anginal attacks are attributed (quite reasonably) to coronary arterial spasm. In a second group of nine patients high grade fixed coronary arterial stenosis is considered the pathogenetic mechanism for the attacks of variant angina. I disagree with this latter conclusion.

Their Table I shows that none of the patients in the group with severe coronary obstruction had a history of angina on

exertion. Moreover, the authors did not document whether attacks at rest in this group were associated with tachycardia or elevated arterial pressure, which would increase myocardial oxygen requirements. They have thus failed to explain adequately what actually did cause these patients to have severe myocardial ischemia while at rest.

There is justification for the belief that coronary arterial spasm was the pathogenetic mechanism in most if not all of their cases, even those with high grade fixed obstruction. The elegant angiographic and physiologic observations of Maseri et al.[2,3] are consistent with this view, as are my own angiographic observations in two patients in whom coronary spasm superimposed on high grade fixed stenosis produced transient complete coronary occlusion, which reproduced the symptoms and electrocardiographic changes that had been seen on the ward before arteriography.

In Prinzmetal's variant angina one can find a complete spectrum of coronary obstructive disease from no arteriographically discernible disease to high grade multivessel obstruction. What binds these arteriographically diverse conditions into a distinct clinical syndrome is the recurrent development of localized transmural myocardial ischemia (injury) when myocardial oxygen needs are low, and the usual absence of ischemia when the metabolic needs of the heart are high. The best information available indicates that the proximate cause of this syndrome is coronary spasm whether or not high grade fixed coronary obstruction is also present. The underlying causes of such spontaneous coronary spasm are not known.

This is of clinical importance. Patients with symptoms due to coronary spasm tend to get operated upon when they have some high grade coronary obstructive disease but not when there are no fixed obstructions. This form of treatment may be justified when good medical therapy fails to control symptoms. But the results of coronary bypass surgery are not as good with this syndrome as with classic angina pectoris because coronary spasm often persists after placement of a bypass graft; spasm may involve the vessel distal to the graft or occur in ungrafted vessels, and even may be responsible for thrombosis of the graft. It is possible that some of the unsatisfactory results of surgery in these cases can be avoided by the routine intraoperative administration of vasodilators and by continuing such administration in the postoperative period even in the absence of symptoms. An effective surgical method for abolishing coronary arterial spasm would be an appropriate prelude to bypassing fixed obstruction in these cases, but such a method is currently not known.

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REPLY

The 17 patients in our study had in common the occurrence of chest pain while at rest and S-T segment elevation during painful episodes. Coronary arteriography in nine patients revealed obstructive lesions that, according to current concepts, were sufficiently severe to be responsible for angina under situations of augmented myocardial oxygen requirements. In eight of these nine patients the luminal diameter of at least one coronary artery was narrowed by more than 85 percent. Luminal narrowing of the cross-sectional diameter of a coronary artery by more than 85 percent has been demonstrated in canine preparations to be sufficient to impede distal coronary blood flow at rest.[1] Therefore, it is not possible to state that fixed obstructions of this severity were not solely responsible for episodes of angina. In our minds, and as stated in a recent compilation of knowledge on this subject,[2] spasm as the proximate mechanism of ischemia in all patients with variant angina is not as clearly established as MacAlpin apparently believes.

However, we, like MacAlpin, have developed the feeling that coronary arterial spasm, in some instances, is superimposed on significant lesions and have recently documented this notion by coronary arteriography in two patients. Coronary arterial spasm occurred spontaneously during arteriography at the site of a 60 percent stenosis of the proximal left anterior descending coronary artery, resulting in near total occlusion in one patient. In the other patient, spasm appeared at the site of an 80 percent stenosis of the mid right coronary artery, producing total occlusion.

In conclusion, we agree that spasm may be superimposed on lesions of any severity. However, given the current state of knowledge on this topic, one can be relatively confident that spasm is the responsible mechanism eventuating in myocardial ischemia only in those patients with clearly nonsignificant fixed stenoses.

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Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Department of Continuing Education Programs, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, Calif.

1976

DEC. 7–10 — **Coronary, Valvular and Myocardial Heart Diseases: Structure-Function Correlations.** William C. Roberts, FACC, director. Williamsburg Lodge, Williamsburg, Va.

DEC 10–12 — **The Ninth Annual Cardiovascular Symposium—Cardiology for the Clinician—1976: Facts, Fables and Fallacies.** Henry I. Russek, FACC, director. Americana Hotel, New York, N.Y.

1977

JAN. 10–14 — **Results and Evaluation of New Methodology in Cardiology.** John H. K. Vogel, FACC, James S. Forrester, FACC and Bruce C. Paton, FACC, directors. Opticon Theater, Snowmass - at - Aspen, Aspen, Colo.

JAN. 17–20 — **Core Curriculum: Pediatric Echocardiography.** Richard A. Meyer and Samuel Kaplan, FACC, directors. Children's Hospital, Cincinnati, Ohio

JAN. 21–23 — **Clinical Strategies in Ischemic Heart Disease: New Concepts and Current Controversies.** H. J. C. Swan, FACC and Eliot Corday, FACC, directors. Century Plaza Hotel, Los Angeles, Calif.

MAR. 7–MAR. 10 — **Twenty-sixth Annual Scientific Session.** Charles Fisch, FACC, president. Las Vegas Hilton Hotel and Sahara Hotel, Las Vegas, Nevada

MAR. 17–19 — **Contemporary Management of Acute Myocardial Infarction by the Family Physician.** Robert S. Eliot, FACC, director and James G. Jones, William P. Nelson, FACC and Thomas A. Nicholas, co-directors. Hay Adams Hotel, Phoenix, Ariz.

MAR. 17–19 — **Cardiovascular Disease—1977: Practical Diagnosis and Management.** John Ross, Jr., FACC, Joel S. Karliner, FACC and Kirk L. Peterson, FACC, directors. Hotel Del Coronado, Coronado, Calif.

MAR. 24–26 — **The Pathology of the Heart.** Maurice Lev, FACC and Jesse E. Edwards, FACC, directors. Palmer House, Chicago, Ill.

MAR. 28–APR. 1 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, Ind.

APR. 4–13 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC, James E. Crockett, FACC and Arthur D. Hagan, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, Calif.

APR 13–15 — **Echocardiography for the Clinician.** Nathaniel Reichek and Joel Morganroth, FACC, directors. The Hilton Hotel of Philadelphia, Pa.

APR 13–15 — **Vectorcardiography: Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, Ariz.

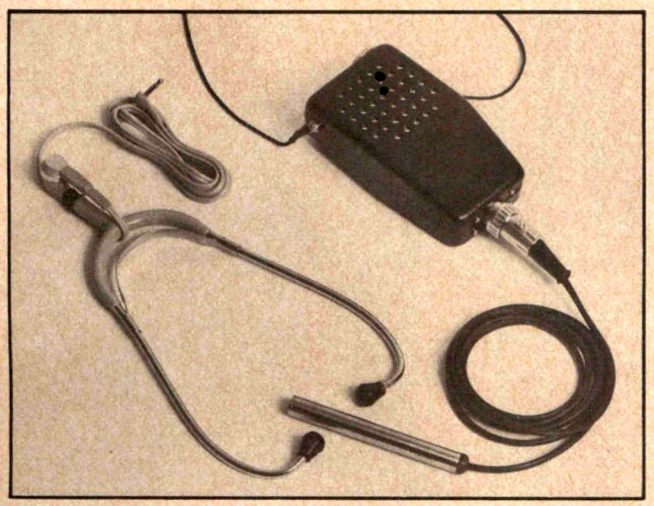
APR. 18–22 — **Consultant's Course in Cardiology.** Simon Dack, FACC, director and Michael V. Herman, FACC, Richard Gorlin, FACC and Louis E. Teicholz, FACC, co-directors. Mount Sinai Medical Center, New York, N.Y.

APR. 25–28 — **A Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, Fla.

APR. 28–30 — **New Approaches to Cardiac Diagnosis.** Arthur Selzer, FACC and Keith E. Cohn, FACC, directors. Hyatt Hotel on Union Square, San Francisco, Calif.

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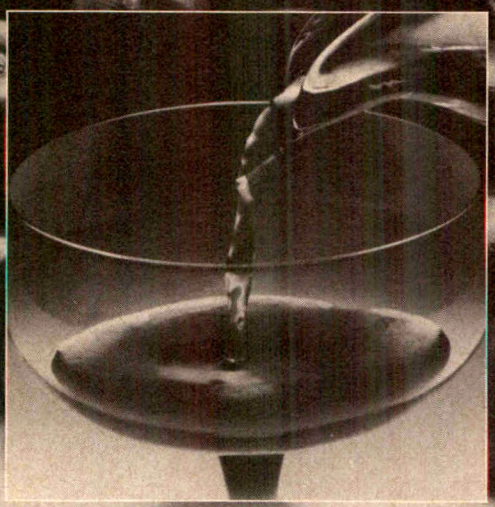
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A59

FOR PATIENT COMPLIANCE

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KLORVESS® 10% LIQUID

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Klorvess® Combined Brief Summary

Klorvess (potassium chloride) 10% Liquid

Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol, 1%.

Klorvess Effervescent Tablets

Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove-plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration:

Klorvess® Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess® (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in 16-ounce and gallon bottles.

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...OR WHATEVER



THE SUBTLE MIXER

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Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g.

Delicious cherry-with-pit flavor. If you've tasted it, you know KLORVESS® (potassium chloride) 10% Liquid provides a delicious natural flavor. So good, in fact, that it should be mixed only with water.

Or whatever flavor your patients like . . . because the taste of KLORVESS® Effervescent Tablets is determined by what they're mixed with. The subtle mixer.

Convenience in therapeutic doses. Both forms of KLORVESS offer 20 mEq potassium chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS 10% Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

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Hypertension

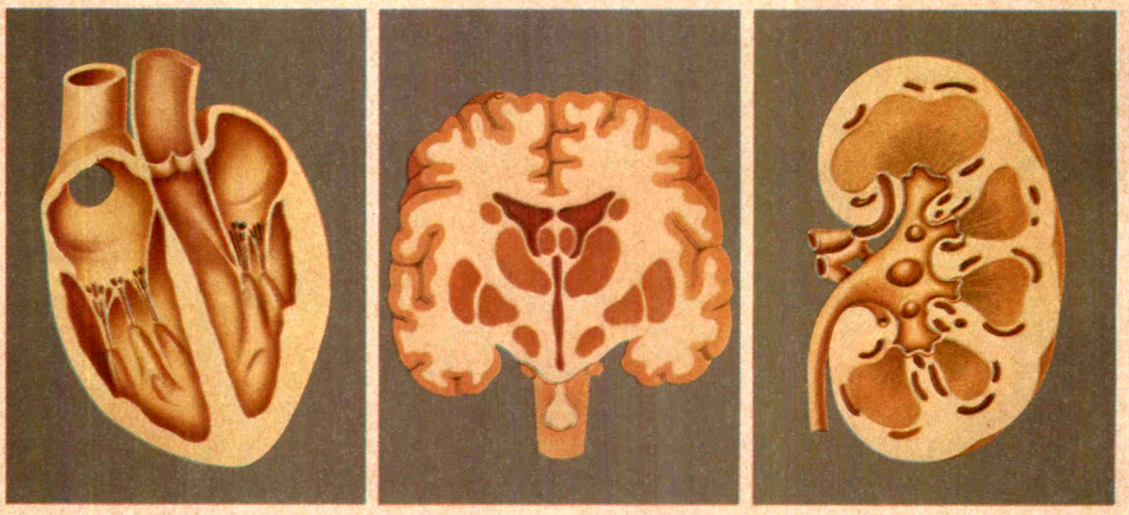
An important new indication for

Inderal®

Brand of

propranolol hydrochloride

Tablets 10 mg, 40 mg, 80 mg



Hypertension: a new indication for Inderal

Inderal (propranolol hydrochloride) is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. Inderal is not indicated for treatment of hypertensive emergencies.

Actions of Inderal

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Mechanism of antihypertensive effects

The mechanism of the antihypertensive effects of Inderal has not been established. Among the factors that may be involved are:

(1) decreased cardiac output,



(2) inhibition of renin release by the kidneys, and



(3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.



Inderal dosage must be individualized

■ The initial dose is 80 mg Inderal daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved.

■ The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required.

■ The time course of full blood pressure response is variable and may range from a few days to several weeks.

■ Inderal is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When Inderal is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

How Inderal is supplied

TABLETS

—Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000.

—Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000.
(See HOW SUPPLIED section information on following pages.)



Before prescribing Inderal for hypertension, please read the full prescribing information on the following two pages.

Ayerst

(For full product information, see package circular.)

INDERAL®
Brand of propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Additional carcinogenicity studies in rats and mice conforming to recently accepted protocols are nearing completion and no drug-related increase in tumors has been observed.

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias. Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS

Hypertension

INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis

The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL (propranolol hydrochloride) exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

Cardiac Arrhythmias

1.) Supraventricular arrhythmias
   a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.)
   b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient.
   c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.)
   d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
   e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias
Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias.
   a) Ventricular tachycardias
   With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.*
   b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication
If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)
Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia
Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL (propranolol hydrochloride) may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis

INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depress-

ing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL (propranolol hydrochloride) therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.* isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM *(e.g.,* CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL (propranolol hydrochloride) may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects (fetal resorptions) have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

HYPERTENSION—*Dosage must be individualized.*

The initial dose is 80 mg INDERAL daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved. The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required. The time course of full blood pressure response is variable and may range from a few days to several weeks. INDERAL is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When INDERAL is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

ANGINA PECTORIS—*Dosage must be individualized.*

Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA — *Preoperatively* —60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

(propranolol hydrochloride)

TABLETS

—Each tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0461-81) and 1,000 (NDC 0046-0461-91). Also in unit dose package of 100 (NDC 0046-0461-99).

—Each tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0464-81) and 1,000 (NDC 0046-0464-91). Also in unit dose package of 100 (NDC 0046-0464-99).

—Each tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 (NDC 0046-0468-81) and 1,000 (NDC 0046-0468-91). Also in unit dose package of 100 (NDC 0046-0468-99).

INJECTABLE

—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10 (NDC 0046-3265-10).

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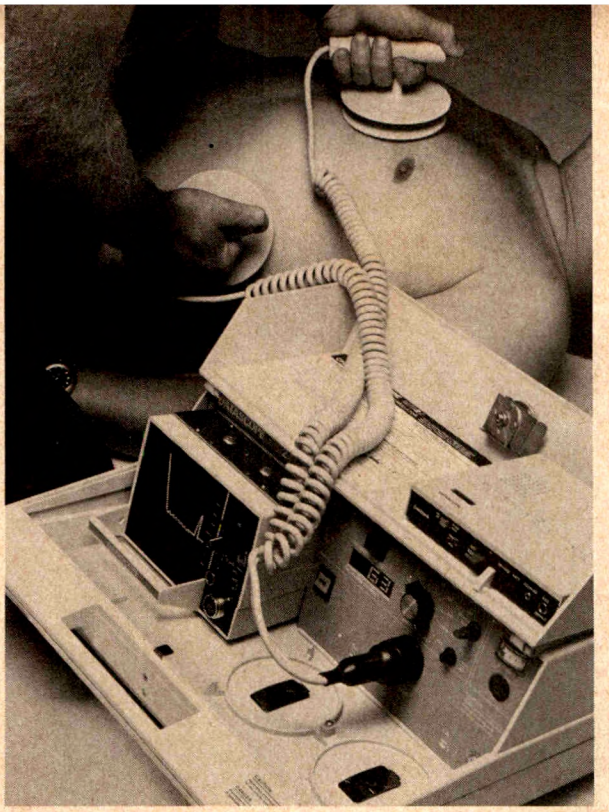
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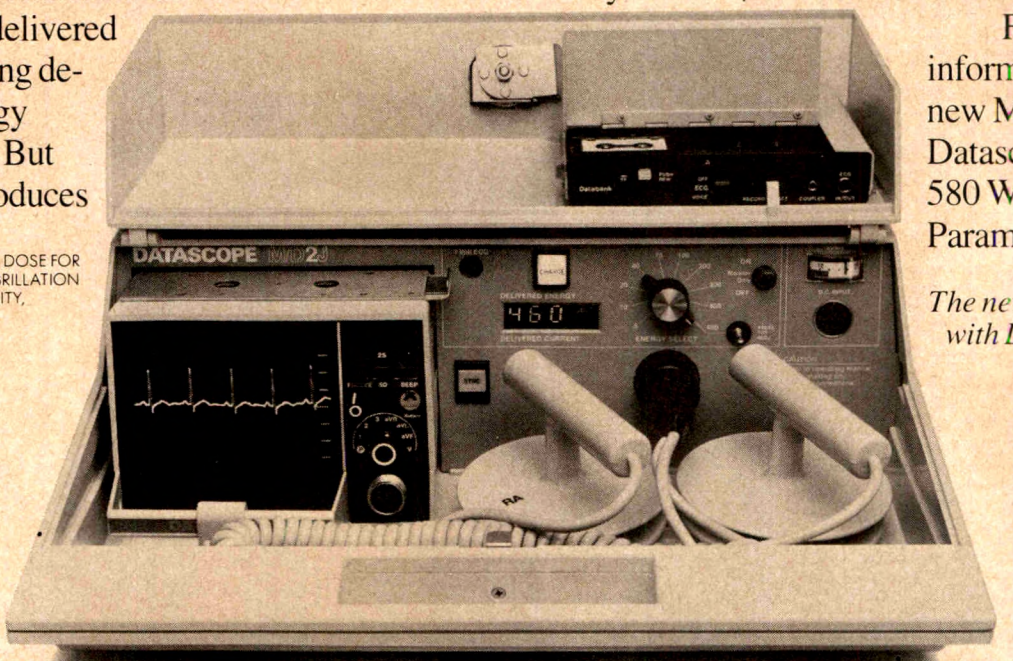
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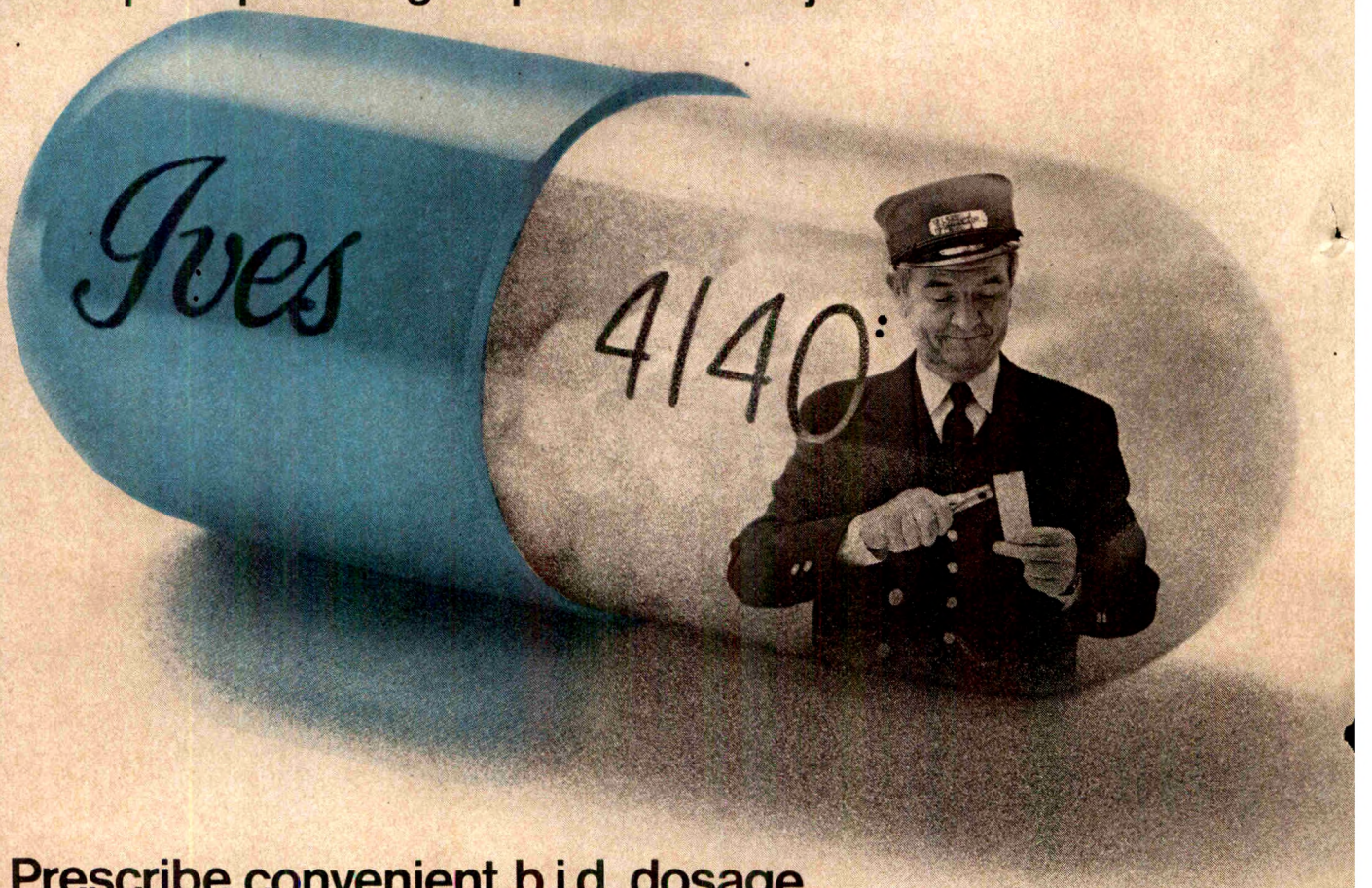
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*ACKER, JR., W.A.: ELECTRICAL DOSE FOR DEFIBRILLATION. CARDIAC DEFIBRILLATION CONFERENCE, PURDUE UNIVERSITY, PGS. 121-7, OCT. '75.

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Dosage: Every 6 to 12 hours according to need.

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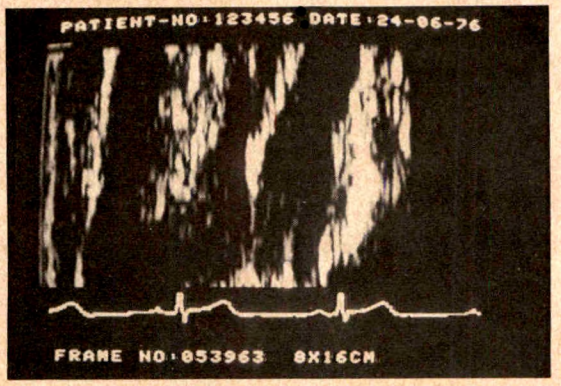
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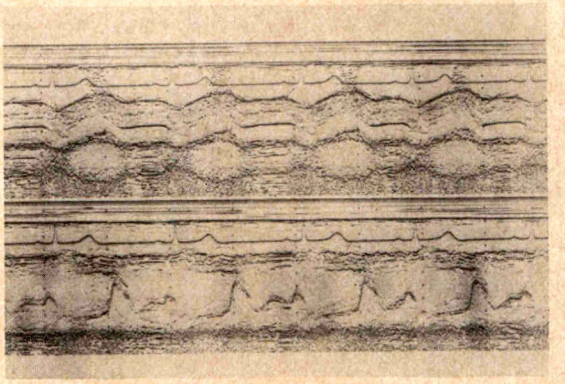
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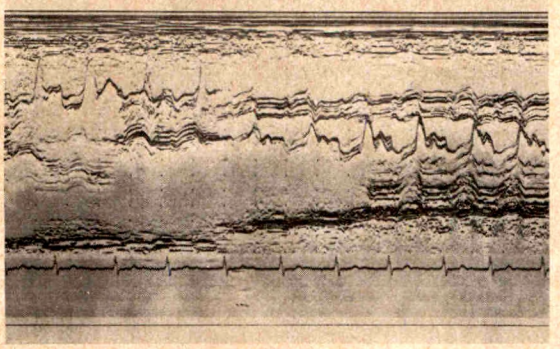
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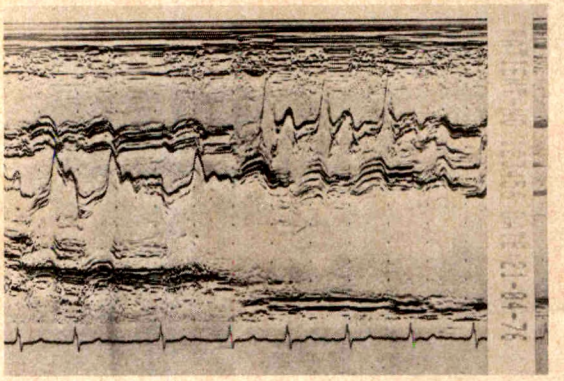
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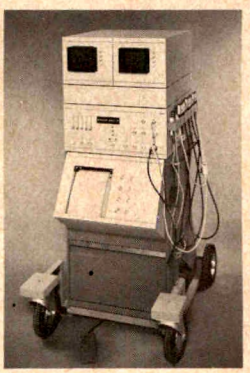


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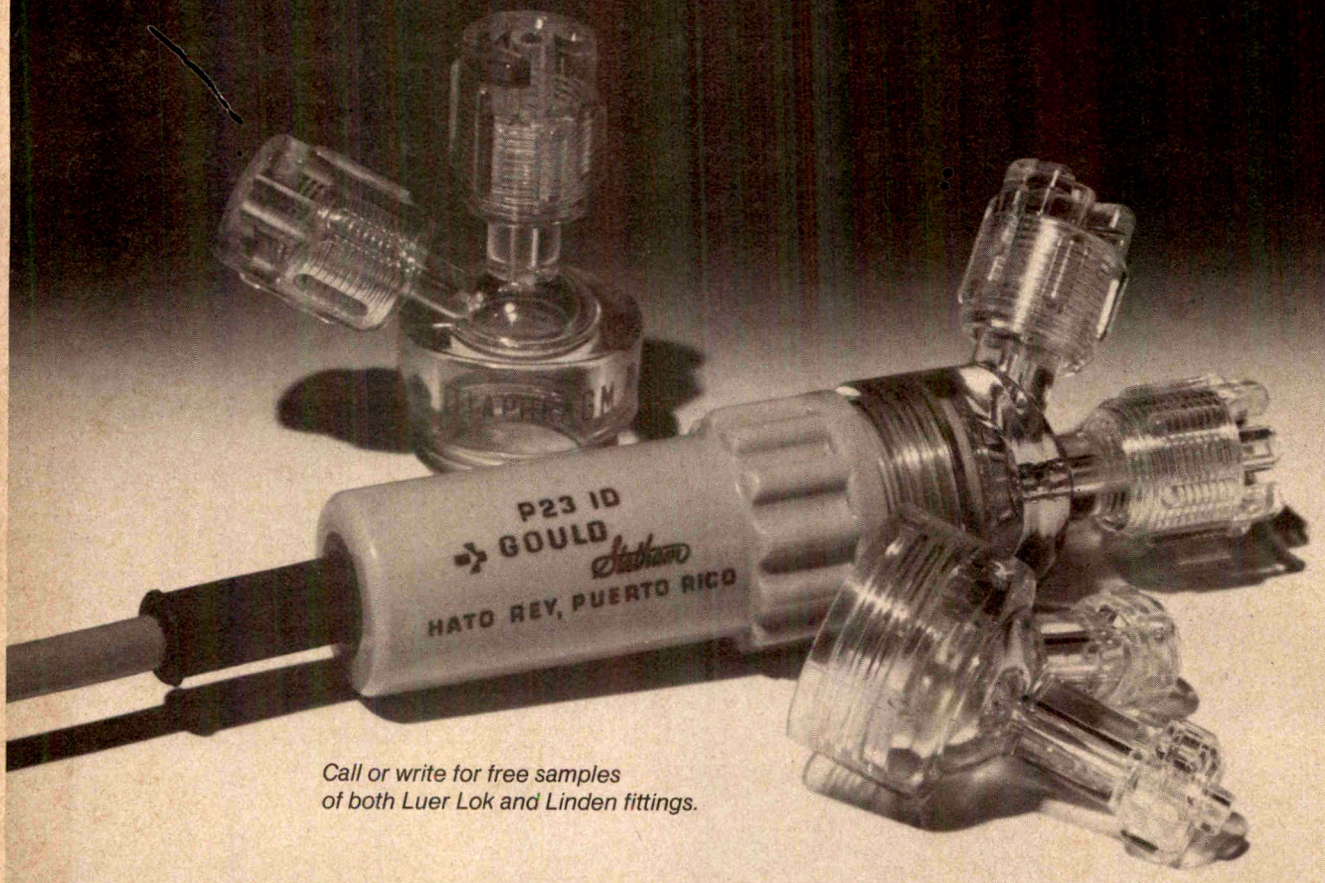
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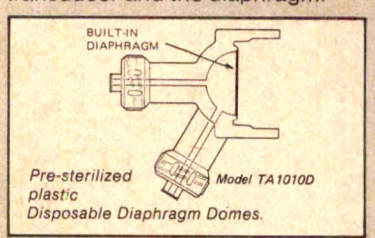
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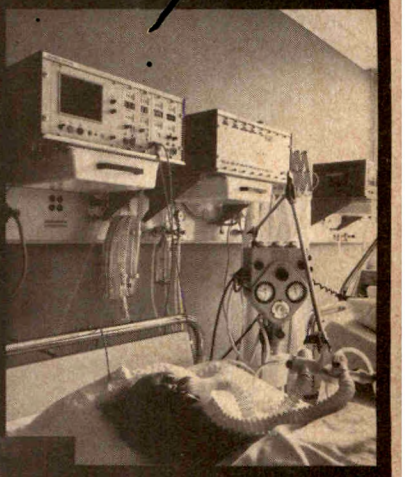
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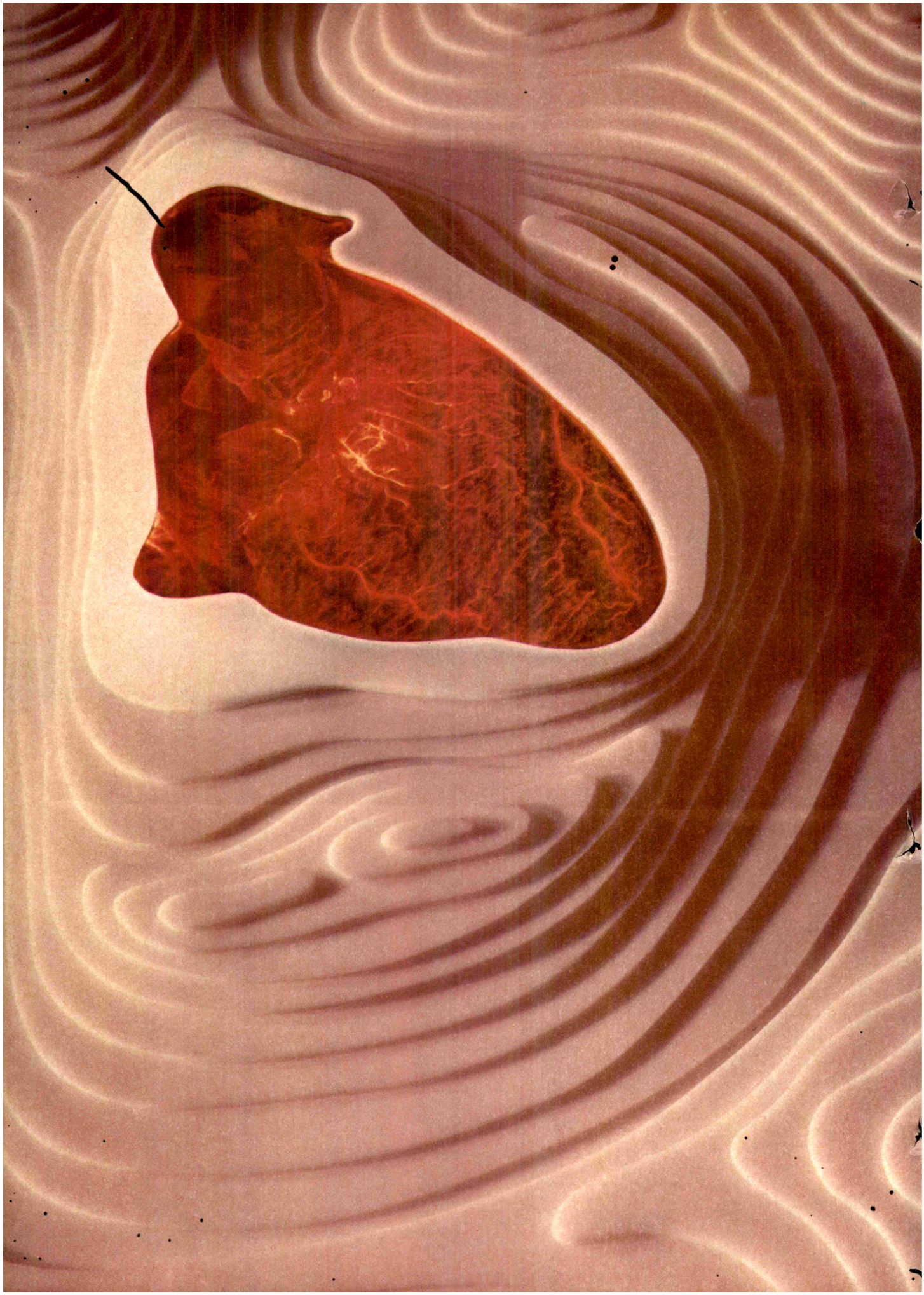


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Contraindications: Recent myocardial infarction, severe anemia, glaucoma, increased intracranial pressure, idiosyncrasy, hypotension.
Precautions: For ORAL, not sublingual, use. If blurring of vision or dryness of mouth occurs, discontinue drug. Tolerance may develop on long-term usage.
Adverse Reactions: Occasional transient headaches. Overdoses may cause flushing, headaches, tachycardia, dizziness.
Dosage: One capsule two or three times daily at 8 to 12-hour intervals.

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A Kendall Research Report

Clinical Studies prove T.E.D.® Anti-Embolism Stockings reduce the incidence of Deep Vein Thrombosis.

1.

	Non-Stocking	Stocking*
Legs	63	63
Incidence of DVT	21	5

*T.E.D.® Anti-Embolism Stockings

2.

	Control Group Non-Stocking	Test Group Stockings*
Incidence of DVT	50%	25.5%

*T.E.D.® Anti-Embolism Stockings

Two recently completed studies provide clinical evidence that T.E.D. Anti-Embolism Stockings effectively reduce the incidence of deep vein thrombosis (DVT).

In one study, I^{125} fibrinogen was used to measure the incidence of DVT in 63 patients undergoing major abdominal surgery. One leg of each of the patients was fitted with a T.E.D. Anti-Embolism Stocking. The other was left non-compressed.

Scanning of the patients revealed over four times as many cases of deep vein thrombosis in the non-stocking group as in the stocking group.[1]

In the other study, radioactive I^{125} fibrinogen was also used. Seventy major surgical patients were divided into two groups matched for age, type of operation, duration of operation, and incidence of malignancy. One group was fitted with T.E.D. Anti-Embolism Stockings pre-operatively. The control group was non-compressed.

The results showed that T.E.D. Anti-Embolism Stockings reduced the incidence of DVT by half.[2]

For a more detailed account of the two studies and reports on other recent research, write The Kendall Company, One Federal Street, Boston, Mass. 02101. Attention: T.E.D. Product Center.

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INNOVATORS IN PATIENT CARE

1. Ibrahim, S. Z., Scurr, J. H., and LeQuesne, L. P. "The Effect of Graded Compression (TED) Stockings on the Incidence of Post-Operative Deep Vein Thrombosis." Eleventh Congress of the European Society for Surgical Research, Dublin 1976.
2. Holford, C. P., and Bliss P. M., "The Effect of Graduated Static Compression on Isotopically Diagnosed Deep Vein Thrombosis of the Leg." Surgical Research Society, Winter Meeting, Royal College of Surgeons, January 1976.

CONTRAINDICATIONS Stockings may not be recommended for patients with the following:

1. Any local leg condition in which stockings would interfere, such as: a. dermatitis, b. vein ligation (immediate post-operative), c. gangrene, d. recent skin graft.
2. Severe arteriosclerosis or other ischemic vascular disease.
3. Massive edema of legs or pulmonary edema from congestive heart failure.
4. Extreme deformity of leg.

PRECAUTIONS:

1. Proper sizing and application must be assured.
2. For full-leg style T.E.D.'s, avoid interference of side panels or waistband with incisions, drainage tubes, catheters, or other exterior devices.

CAUTION: Federal law restricts this device to sale by or use on the order of a physician.

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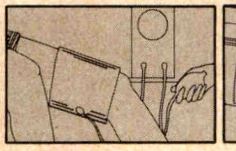
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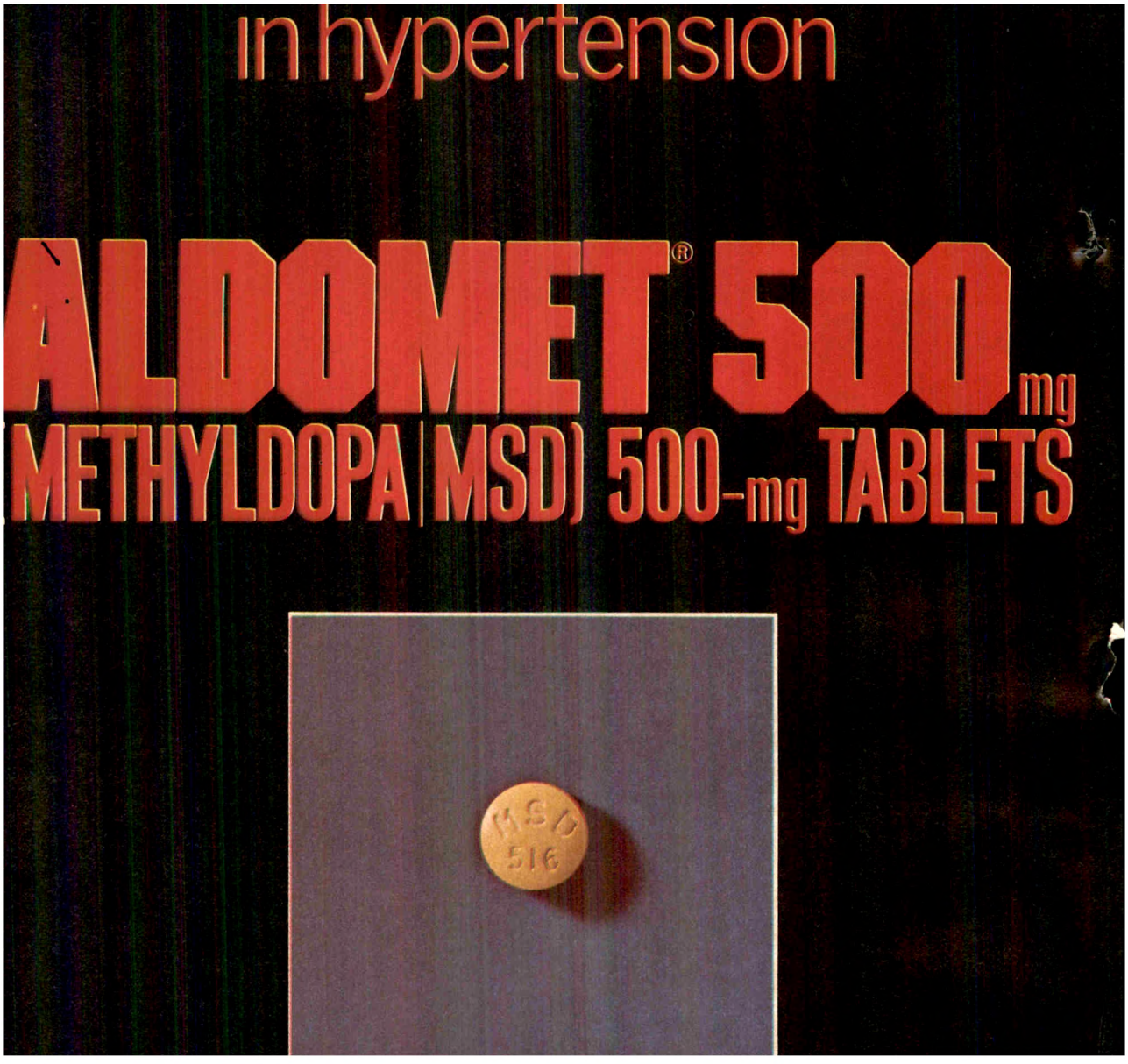
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in hypertension
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[METHYLDOPA | MSD] 500-mg TABLETS
MSD
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ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

For more details see the brief summary of prescribing information.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

addendum

MSD
MERCK SHARP & DOHME

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

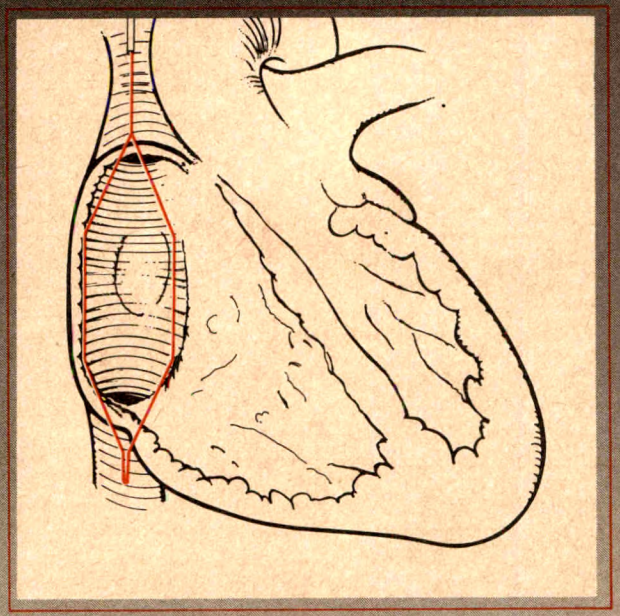
- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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INDICATIONS: USCI® Temporary Atrial Pacemaker Electrodes are designed for intracardiac EKG and temporary transvenous pacing of the heart via external pulse generator.

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The capture threshold may rise over a period of days and the milliamperage output may need to be increased with longer-term atrial pacing.

NOTE: It is recommended that patients be anticoagulated with heparin during the time the wire is left in place. This is based on the observation of very small thrombi or fibrin strands on the end of the atrial pacemaker at the time of the removal; these have been noted with or without heparinization. While clinically apparent pulmonary emboli have not been noted, the possibility of small emboli travelling to the lungs cannot be excluded. As a result, patients paced for more than a few hours have been anticoagulated as a matter of practice.

The T.A.P.E. is designed for a single patient usage only; resterilization is not recommended in view of the uncertainties with respect to insulation degradation, fatigue of electrode structure after sterilization and reuse, etc.

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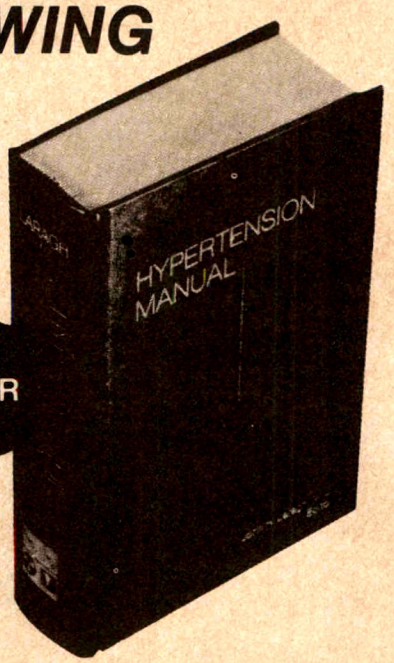
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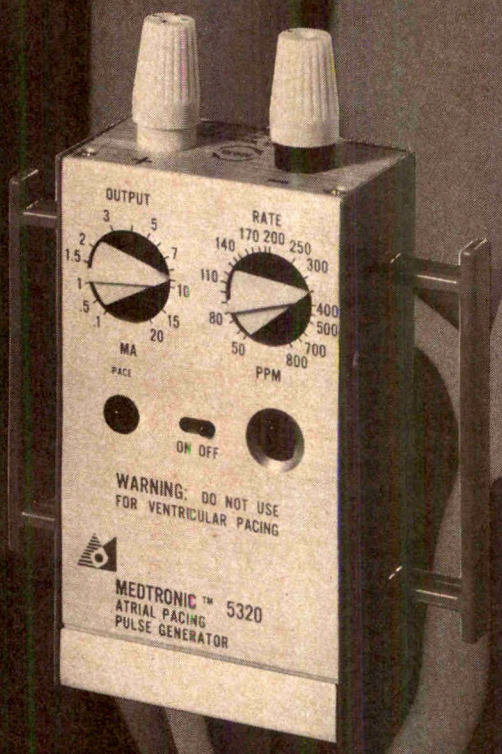
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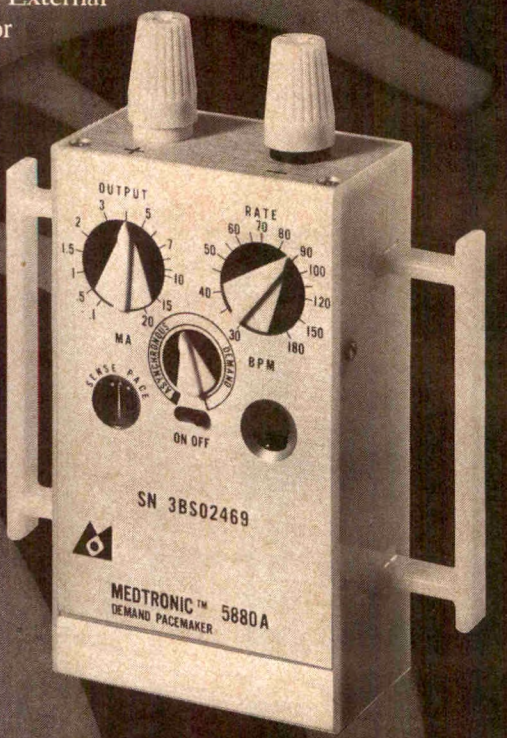
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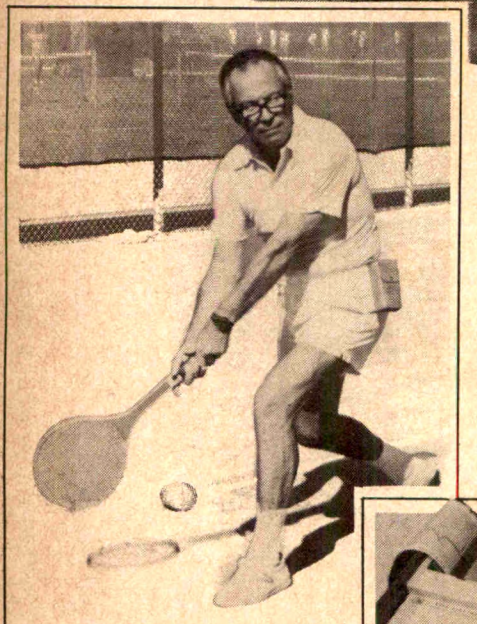
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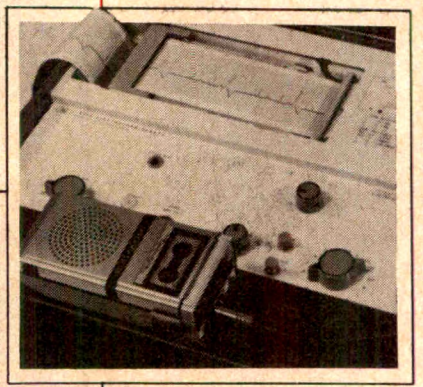


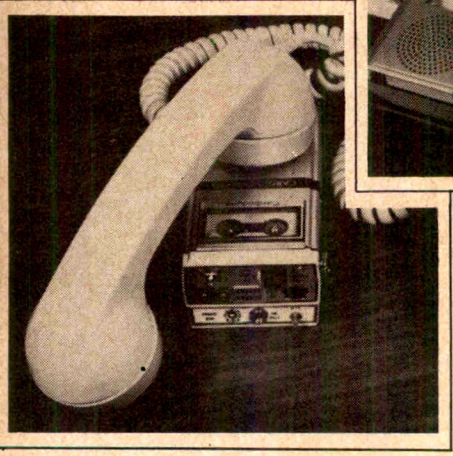
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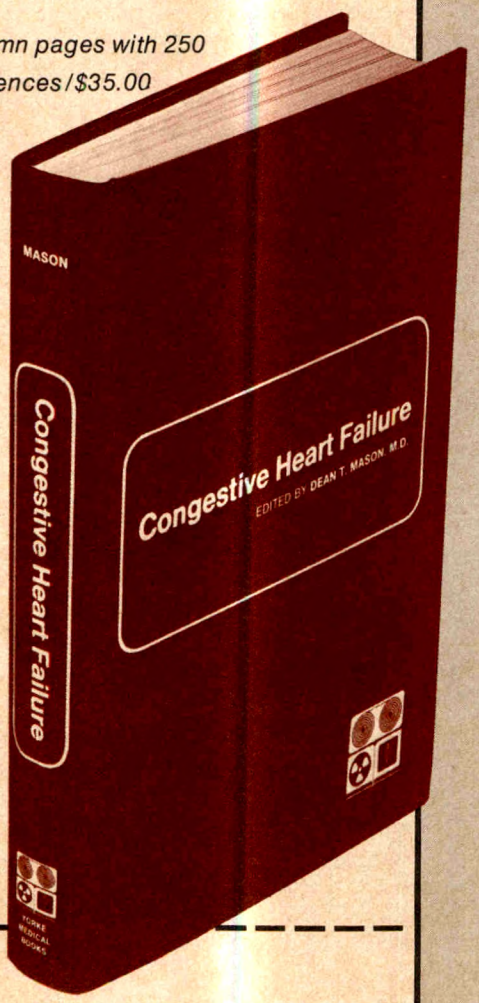
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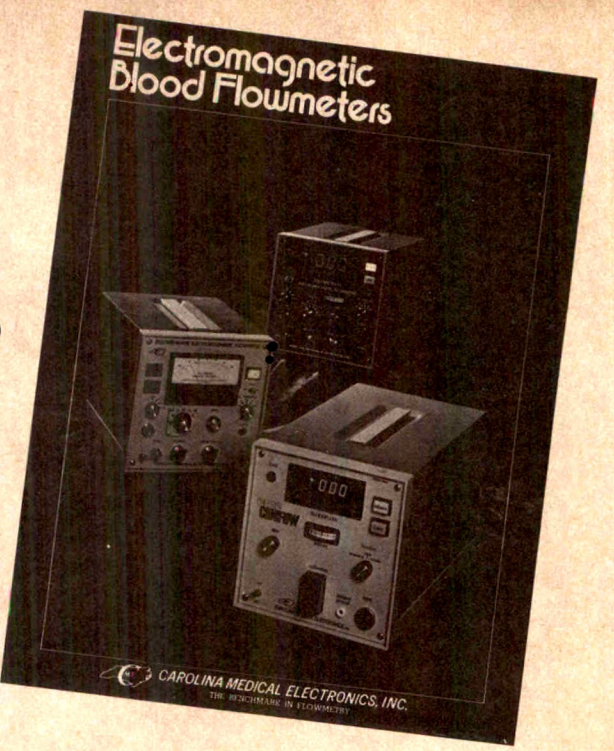
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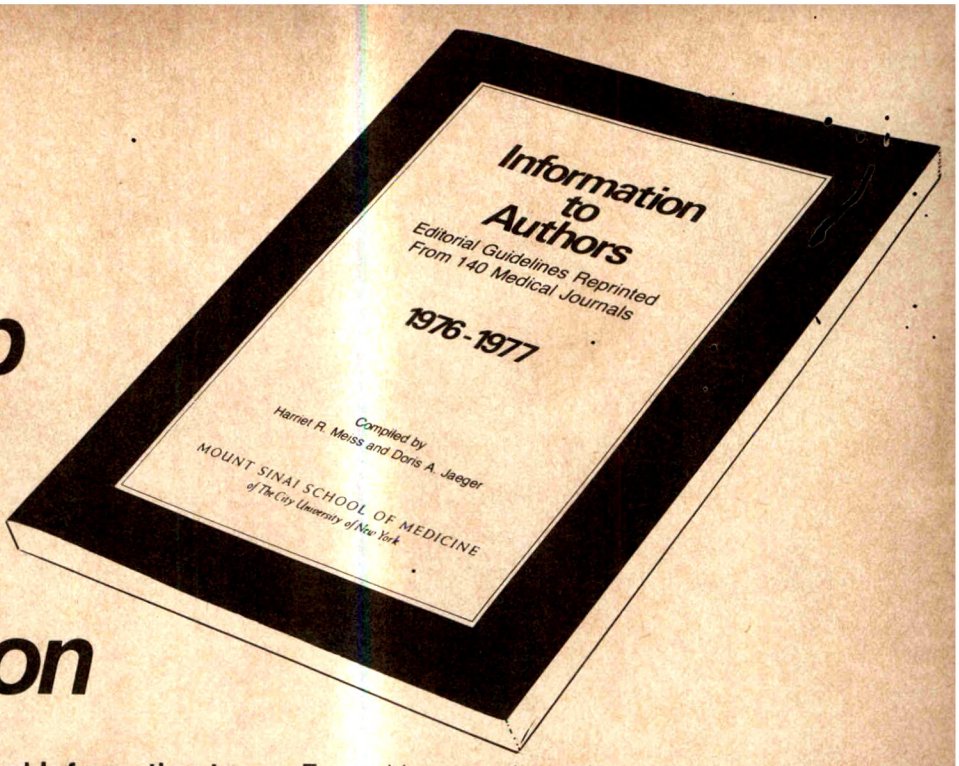


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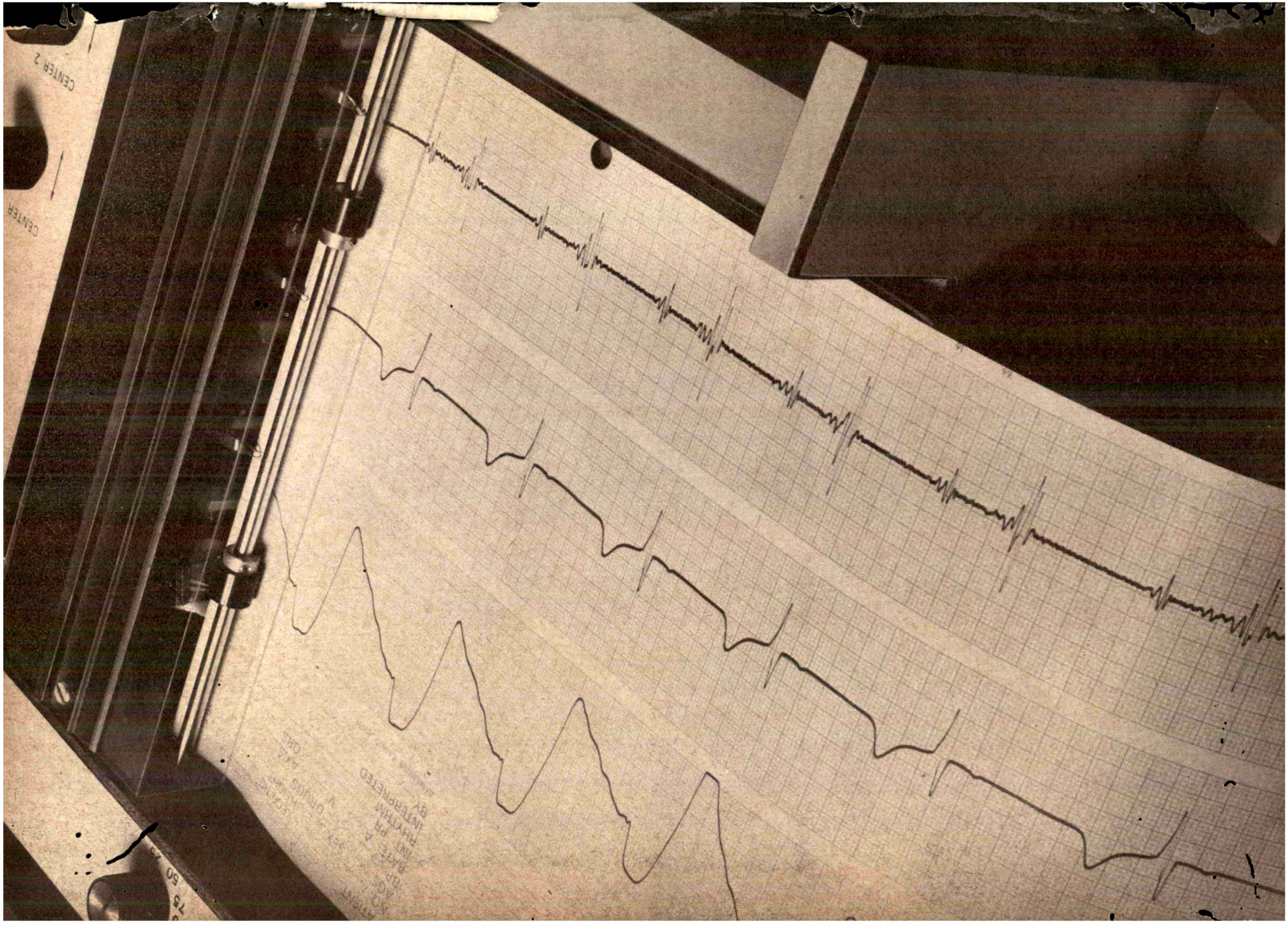
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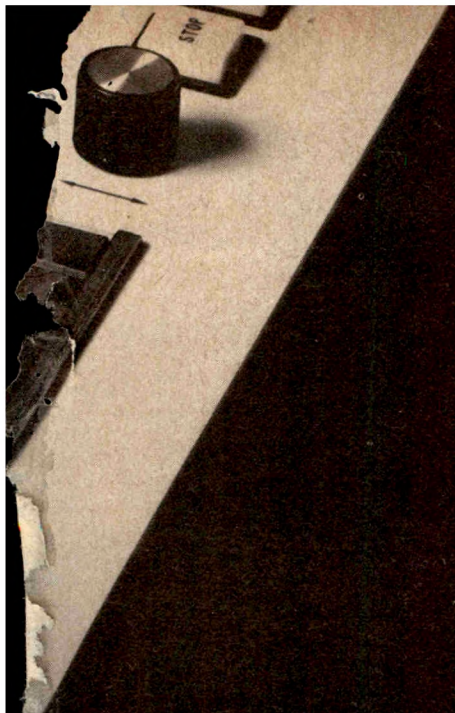
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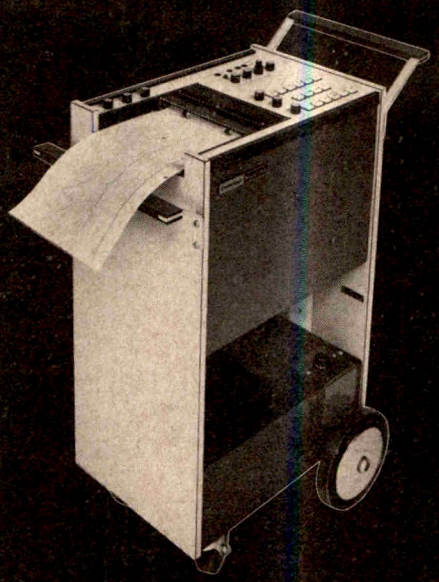


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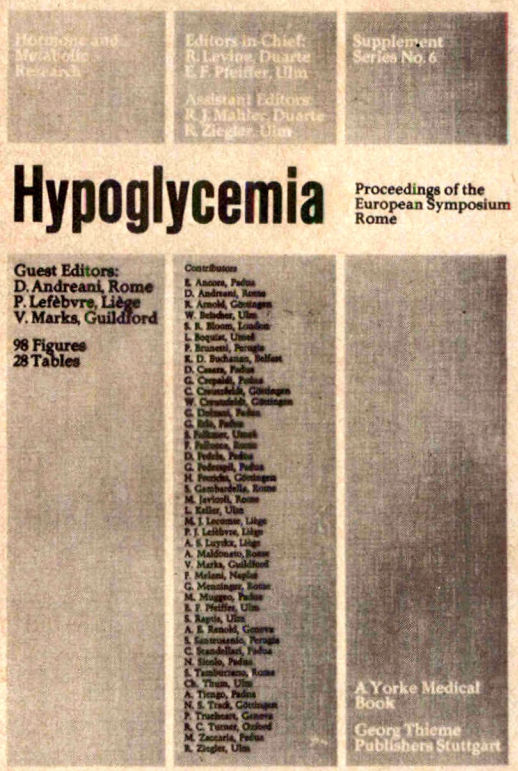
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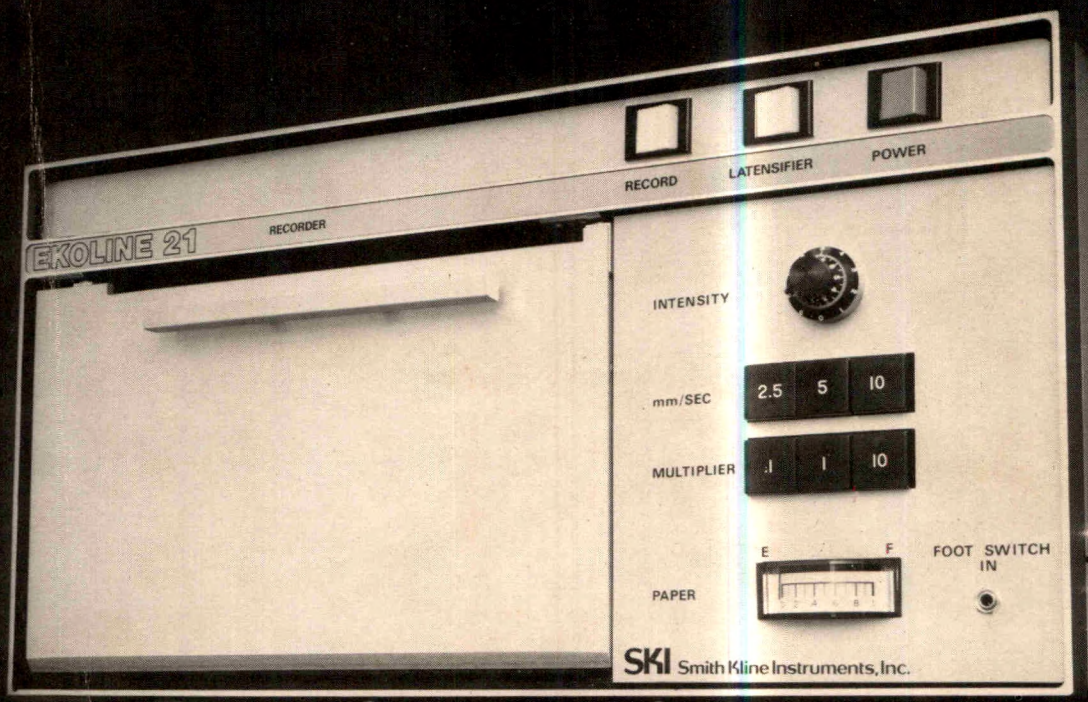
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